Summary Final Report

PROPHYLACTIC MEASURES FOR CENTRAL NERVOUS SYSTEM OXYGEN POISONING IN REST AND EXERCISE

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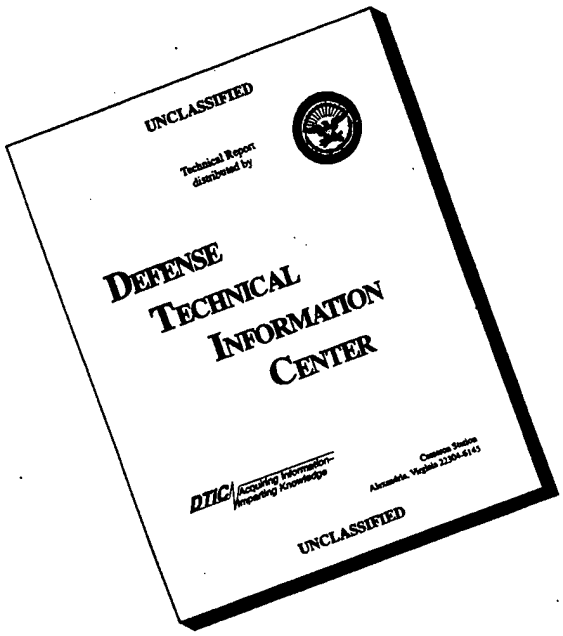

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INTRODUCTION AND BACKGROUND

Central nervous system oxygen convulsions and decompression sickness are related major hazards of operational self-contained diving. The U.S. Navy imposes limits upon oxygen diving, use of oxygen in other forms of self-contained diving, use of oxygen to improve decompression procedure, and use of oxygen to treat decompression sickness. The need exists to increase safety as well as diving depths and durations, and to increase the scope and effectiveness of all forms of self-contained diving operations. The key to success involves delaying or preventing the occurrence of oxygen-induced convulsions during physical underwater work. This has not been accomplished operationally during the past fifty years of self-contained diving.

Critical questions unresolved during the past fifty years have been:

(a) Why physical exercise drastically reduces both the oxygen exposure pressures and the exposure durations capable of causing the convulsions of oxygen poisoning (1-3).

(b) The bases for individual variability in latency of oxygen convulsions (1-3).

(c) Whether immersion itself reduces CNS tolerance to hyperoxia (1-3).

Investigations of these questions and related issues have been the primary objectives of a multiyear Research Program at the Institute for Environmental Medicine (IFEM), the results of which are available within the Environmental Biomedical Research Data Center (4). Prior to the period of this Summary Report, an extensive investigation of possible mechanisms for adverse exercise effects on human CNS tolerance to oxygen exposure at 2.0 ATA was performed (5). Oxygen exposure conditions and exercise workloads were purposely selected to complement the practical in-water oxygen tolerance trials previously performed at the Naval Experimental Diving Unit (NEDU) by Butler and Thalmann (6,7).

A potential mechanism for the detrimental effects of exercise on CNS oxygen tolerance was provided by the discovery that ventilatory responses to incremental exercise during oxygen breathing at 2.0 ATA were suppressed to a degree that allowed arterial Pco_2 to rise nearly linearly with increasing workload (Fig. 1) (5), rather than falling progressively at higher workloads as occurs during air breathing at 1.0 ATA (8,9). Previous studies have shown that cerebral blood flow (CBF) increases sharply with rising arterial Pco_2 (10,11), and that hypercapnia-induced increments in

CBF during oxygen breathing at high pressure cause prominent elevations in brain oxygen pressure (12). On this basis, the operational significance of the data shown in Fig 1 is that an associated increment in CBF, likely to accompany such hypercapnia, should deliver a higher oxygen dose to the brain and accelerate the onset of convulsions. Quantitative investigation of this potential was a major focus of the research summarized in this Report.

Another focus of the research in this Report was stimulated by an unexplained difference between selected results of the NEDU oxygen tolerance trials (7) and the more recent IFEM studies (5) of exercise effects on CNS oxygen tolerance (Fig. 2). One of the profiles studied by Butler and Thalmann involved a 30-min oxygen exposure at 35 fsw (2.06 ATA) while exercising continuously at an average O_2 uptake of 1.66 L/min. Four of 40 divers developed leg twitching at 25-30 min to give a 10% incidence of definite CNS symptoms. In the IFEM studies, 10 men breathing oxygen at 2.0 ATA tolerated two 30-min periods of exercise at an average workload of 1.87 L/min with no indications of increased neuronal excitability, incipient convulsions, decrement in mental function, or other manifestations of CNS oxygen toxicity. An intentional difference in design between the two correlated studies was that the NEDU divers worked underwater, while the IFEM subjects performed exercise in a dry chamber. Based on the hypothesis that physiological responses to immersion could account for the different results shown in Fig. 2, the effects of partial and total immersion on ventilatory, arterial Pco_2, and CBF responses to CO_2 inhalation and incremental exercise were studied extensively. Results of these measurements are summarized in this Report.

PROGRAM PURPOSES

(a) To identify and measure quantitatively in humans the physiologic and environmental influences that increase or decrease the toxic dose of oxygen in brain tissue at rest and during exercise.

(b) To use observed physiologic effects to decrease brain oxygen pressure purposefully, thereby delaying occurrence of hyperoxic convulsions at rest and in work.

(c) To increase safe duration limits for inspired oxygen at desired operational diving depths, while using O_2 and/or N_2-O_2 or He-O_2 breathing gas.

(d) To improve safety and versatility of all decompression methods through improved CNS tolerance to hyperoxia.

METHODS

The planned investigation of adverse exercise effects on CNS oxygen tolerance at 2.0 ATA required the validation of a reliable method for measuring CBF responses to exercise in a hyperbaric chamber. At the outset of this study, the availability of transcranial doppler ultrasonography provided a noninvasive method that could be used to measure blood flow velocity in the middle cerebral artery (MCA). However, it could not be assumed that MCA diameter would remain constant during exposure to hypercapnia and exercise. In order to validate this method for use as a CBF index, MCA blood flow velocity was measured concurrently with CBF, as determined by clearance of radioactive xenon, over a wide range of arterial Pco_2.

Additional technical requirements were imposed by the planned investigation of immersion effects on physiological responses to hypercapnia and exercise. An underwater work-measurement system was designed and constructed. Rates of oxygen uptake were measured over similar ranges of underwater and dry workloads. Specific adaptations of transcranial doppler ultrasonography were also required for underwater use. Technical preparations and development of methods are described below.

Establishment of Quantitative, On-Line Method for Continuous Measurement of Brain Blood Flow

Transcranial doppler measurements of MCA blood flow velocity were calibrated against simultaneous measurements of CBF by ^{133}Xe clearance (Fig. 3). Eight subjects were studied over an arterial Pco_2 range of 25 to 50 mm Hg while breathing oxygen as the background gas. Arterial Pco_2 was reduced by controlled hyperventilation and increased by breathing 4% and 6% CO_2 in O_2. Individual CBF-velocity relationships for all 8 subjects at 4 levels of arterial Pco_2 are shown in Fig. 3, along with the parabolic curve that best describes the overall relationship. The equation of the parabola and 95% confidence limits about the curve are also shown.

As an alternative to the parabolic expression relating CBF to MCA blood flow velocity (Fig. 3), CBF and velocity have a linear relationship at increased levels of arterial Pco_2 when expressed as percent changes from control values measured while breathing 100% O_2 (Fig. 4). The solid line in Fig. 4 is a regression line through 16 individual points at increased levels of arterial Pco_2 with the intercept set at zero. The equation for the regression line is also shown. The dashed diagonal represents the line of equal changes for both parameters. The observation that CBF increments consistently exceed corresponding velocity changes is consistent with MCA vasodilation during exposure to hypercapnia.

Development of Laboratory Underwater Ergometry System for Controlled Hyperoxic Exercise

An underwater work-measurement system was developed to measure physiological responses to equivalent exercise workloads under dry and immersed conditions (Fig. 5). The system was calibrated in 8 subjects by measuring oxygen uptake at underwater workloads of 30, 50, 75, 100, 125, and 150 watts and dry workloads of 30, 50, 100, 150, and 200 watts. Calculated regression lines fitted to oxygen uptake values obtained under wet and dry conditions had nearly identical slopes with the wet values about 0.550 L/min higher than the dry values at the same ergometer workload settings (Fig. 6). The influence of pedal rate on oxygen uptake at equivalent workloads under wet and dry conditions was also evaluated in 8 subjects (Fig. 7). As expected, the change in oxygen uptake for different pedal rates underwater was much steeper than that found under dry conditions. A pedal rate control system with an underwater speaker that emitted low or high tones when pedal rate was too low or too high, respectively, was used to provide feedback that helped the subject to maintain a constant pedal rate underwater.

Development of On-Line Methods for Measuring Physiological Responses in Fully Immersed Subjects

Transcranial doppler ultrasonography is a relatively new technique that was developed initially for use in patients with neurological diseases (13). Prior to the current application, it had never been used for underwater measurements. Many problems were encountered related both to stabilization of the transcranial doppler probe and to the elimination of artifacts caused by multi-directional transmission of doppler signals.

Stable orientation of the probe with respect to the MCA must be maintained at rest and during exercise throughout an experiment to obtain accurate measurements of blood flow velocity. The platform supplied by the manufacturer for long-term attachment of the transcranial doppler probe to an appropriate cranial "window" did not provide adequate stability during exercise even in a dry environment. This problem was solved by the design and fabrication of a new platform that could be attached to the subject's skull with the aid of Stomahesive and double-backed tape. The new platform also provided a mechanism for clamping the transcranial doppler probe to maintain a constant angle of insonation with the MCA. Although Stomahesive worked well in a dry environment, initial immersion testing indicated that it softened underwater. After many unsuccessful attempts to stabilize the probe-platform assembly with elastic straps and waterproof adhesives, it was learned that the softening of Stomahesive underwater occurred slowly enough that probe stability could

easily be maintained for the duration of an experiment.

Multi-directional transmission of doppler signals underwater caused many problems that do not exist in an air background. Artifacts related to head or wave movements appeared as bursts of noise that distorted or completely obliterated the waveform of the blood velocity signal. Head movements were minimized by positioning the subject to provide mechanical stability that facilitated the performance of ergometer exercise without extraneous body movements. Wave action during exercise was reduced significantly by keeping the water level in the immersion pool as high as possible and by changing the pedal rate from 60 to 50 rpm. Artifacts caused by residual wave action were minimized by placing a wood plank at the water-air interface above the transcranial doppler probe.

The requirement for obtaining arterial blood samples from an immersed subject also imposed a need for special precautions to avoid contamination and possible infection of the puncture wound over and in the radial artery. The skin puncture site was covered with antibiotic ointment prior to sealing the area with a large transparent Tegaderm dressing. Waterproofing of the puncture site was further assured by covering the periphery of the Tegaderm patch and adjacent skin with a layer of liquid silocone rubber.

RESULTS AND DISCUSSION

The overall investigation of potentially adverse influences of exercise and immersion on CNS oxygen tolerance was carried out in several phases. Early phases were performed at 1.0 ATA in parallel with the development of required methods as summarized above. As part of the initial effort, transcranial doppler ultrasonography was used to measure MCA blood flow velocity responses to progressive hypercapnia at rest and during exercise. In addition to providing information about CBF responses to the selected conditions, valuable experience with what was then a relatively new method was gained. The next phase of investigation involved the study of immersion effects on ventilatory and cerebral circulatory responses to progressive hypercapnia and exercise. Finally, ventilatory, arterial Pco_2, and cerebral circulatory responses to incremental exercise under hyperoxic and normoxic conditions at 2.0 ATA were measured.

Ventilatory and Cerebral Circulatory Responses to Hypercapnia during Oxygen Breathing at Rest and during Exercise

Seven subjects were studied at rest and during exercise while breathing 100% O_2, 3% CO_2 in O_2, and 5% CO_2 in O_2. The bicycle ergometer workload of 100

watts produced an average oxygen uptake of about 1.35 L/min. Average arterial Pco_2 ranged from about 38 to 45 mm Hg at rest and from 41 to 52 mm Hg during exercise. Ventilatory responses to hypercapnia were significantly higher during exercise than at rest with nearly parallel slopes in both conditions (Fig. 8). Average MCA blood flow velocity responses to hypercapnia also had similar slopes at rest and during exercise with higher values at corresponding levels of arterial Pco_2 during exercise (Fig. 9).

Effects of Partial and Total Immersion on Physiological Responses to Progressive Hypercapnia While Breathing Oxygen at 1.0 ATA

Eight subjects were studied at rest under dry conditions, then during head-out immersion, and finally during total immersion. Water temperature was maintained at 35°C. In each condition, the subject first breathed air, then 100% O_2, followed by consecutive periods of CO_2 administration at controlled end-tidal Pco_2 levels of 45, 50, and 55 mm Hg. Concurrent measurements on each gas included arterial Pco_2, Po_2, and pH, body temperature, MCA blood flow velocity, ventilation rate, tidal volume, respiratory rate, heart rate, and mean arterial blood pressure.

Average ventilatory responses to progressive hypercapnia were higher under dry conditions than in both immersion states, but the differences were small and not statistically significant (Fig. 10). Neither head-out nor total immersion had a measurable effect on ventilatory responses to hypercapnia at rest.

Relationships of average body temperature to increasing arterial Pco_2 reflect small but consistent differences in the dry and during immersion (Fig. 11). Hypercapnia-induced peripheral vasodilation with increased heat loss to the 25°C ambient air atmosphere probably accounted for the observed 0.4°C fall in body temperature under dry conditions. During head-out and total immersion in 35°C water, body temperature remained stable during exposure to hypercapnia. The observation that average body temperature was about 0.3°C higher during total than during head-out immersion probably reflects the fact that these measurements were obtained after an additional 90 min of immersion in warm water.

Average values for mean arterial blood pressure were consistently lower in both immersion states than under dry conditions at comparable levels of arterial Pco_2 (Fig. 12). Mean blood pressure rose progressively in response to increasing arterial Pco_2 with essentially equal slopes in all three conditions, but average values during immersion were significantly lower by about 7-8 mm Hg. Average heart rate also rose progressively in response to increasing arterial Pco_2 with nearly equal slopes in all three conditions (Fig. 13). Average values in both immersion states were nearly identical during exposure to hypercapnia, and both curves were significantly higher by

about 9-10 beats/minute than average values obtained under dry conditions at the same levels of arterial Pco_2. The nearly linear increments in heart rate and mean arterial blood pressure with increasing arterial Pco_2 probably reflect hypercapnia-induced sympathetic stimulation which may be modified to some extent by the superimposed oxygen-induced bradycardia. The lower arterial blood pressure and increased heart rate observed during immersion are consistent with a mild hypotensive response to heat-induced cutaneous vasodilation in 35°C water and a related reflex increase in heart rate.

Regardless of the physiological basis for the observed effects of immersion on systemic circulatory indices, average MCA blood flow velocity responses to increasing arterial Pco_2 were nearly identical under dry conditions and in both immersion states (Fig. 14). These results were obtained under resting conditions with virtually no doppler signal interference related to immersion of the doppler probe. The observed data indicate that cerebral circulatory responses to hypercapnia at rest are not significantly influenced by either head-out or total immersion.

Effects of Partial and Total Immersion on Physiological Responses to Incremental Exercise While Breathing Air at 1.0 ATA

Eight subjects were studied during incremental exercise under dry conditions, then during head-out immersion, and finally during total immersion. Water temperature was maintained at 32°C. Air was breathed rather than oxygen to facilitate measurements of oxygen uptake during exercise. During exposure to each condition, a 10-min rest period was followed by three 6-min workloads consisting of 60, 110, and 150 watts at a pedal rate of 60 rpm in the dry and 30, 80, and 110 watts at 50 rpm during immersion. Concurrent measurements at each workload included end-tidal Pco_2, MCA blood flow velocity, ventilation rate, tidal volume, respiratory rate, heart rate, and rates of O_2 uptake and CO_2 elimination.

Average ventilatory responses to incremental exercise were nearly identical under dry conditions and in both immersion states (Fig. 15). Average end-tidal Pco_2 values at rest and during incremental exercise for all three conditions are shown in Fig. 16. None of the differences in end-tidal Pco_2 values at equivalent workloads were statistically significant by analysis of variance across all workloads and all three conditions.

Average MCA blood flow velocities in all three conditions increased significantly by about 8 cm/sec on the average during the transition from rest to exercise, but remained essentially constant with further increments in workload (Fig. 17). There were no significant differences in MCA blood flow velocities measured

under dry conditions or in either immersion state.

Effects of Oxygen Breathing and Increased Gas Density on Ventilatory, Arterial Pco_2, and Cerebral Circulatory Responses to Incremental Exercise at 2.0 ATA

Physiological responses to consecutive 6-min periods of exercise at 50, 125 and 200 watts were measured in 9 men initially during air breathing at 1.0 ATA, and on a subsequent day, while breathing 100% O_2 or 10.5% O_2 at 2.0 ATA. Average ventilatory responses at rest and during exercise for all 3 conditions are shown in Fig. 18. Oxygen breathing at 2.0 ATA increased ventilation at rest and reduced the ventilatory response to heavy exercise. With respect to air breathing at 1.0 ATA, the reduced ventilatory response to heavy exercise under normoxic conditions at 2.0 ATA is consistent with increased gas density and work of breathing at the higher pressure.

Average arterial or corrected end-tidal Pco_2 values at rest and during exercise are shown in Fig. 19. Under normoxic conditions, arterial Pco_2 values at 2.0 ATA and equivalent end-tidal Pco_2 values at 1.0 ATA were nearly identical at rest and during light exercise. At the highest workload, arterial Pco_2 rose slightly to 43.4 mm Hg at 2.0 ATA and fell to 40.2 mm Hg at 1.0 ATA in accord with the higher ventilation at that pressure (Fig. 18). During oxygen breathing at 2.0 ATA, arterial Pco_2 fell to 36.2 mm Hg at rest and then increased progressively to 45.9 mm Hg during exercise (Fig. 19). In agreement with the arterial Pco_2 data, average MCA blood flow velocity values for both normoxic conditions were nearly identical at rest and during light exercise, and then diverged progressively at the higher workloads (Fig. 20). During oxygen breathing at 2.0 ATA, blood flow velocity values also paralleled the arterial Pco_2 data by falling to 49.2 cm/sec at rest and then rising progressively to 83.3 cm/sec during heavy exercise.

Brain Oxygen Dose in arterial blood, along a mean brain capillary bed, and in brain venous blood can be calculated at rest and during exercise from measured arterial Po_2 values, changes in MCA blood flow velocity (Fig. 20), and previous measurements (12,14,15) of arterial-venous oxygen content differences across the brain. Calculated brain venous and mean brain capillary Po_2 values are plotted in Fig. 21 against rate of CO_2 elimination as an index of workload. As expected under normoxic conditions, calculated brain venous and mean capillary Po_2 values are similar at rest and rise very little during exercise. While breathing 100% O_2 at 2.0 ATA, the calculated brain venous Po_2 rises from 47 mm Hg at rest to 93 mm Hg at the highest workload. An average value of 67 mm Hg at the intermediate workload agrees well with a value of 61 mm Hg measured directly under similar conditions in a previous group of normal men (15). The calculated mean capillary Po_2 of 142 mm Hg obtained at rest during oxygen breathing represents an oxyhemoglobin saturation

of nearly 100%. The calculated values of 351, 456, and 602 mm Hg obtained during incremental exercise reflect the steep elevations in mean capillary Po_2 that are associated with increasing contents of physically dissolved oxygen.

Effects of oxygen breathing at increased pressures on brain oxygenation at rest and during exercise are shown in Fig. 22. Measured brain arterial Po_2 values are shown on the left. Calculated mean capillary Po_2 values are shown in the center, and calculated or measured brain venous Po_2 values are shown on the right. For purposes of comparison with the present data, average values obtained previously for oxygen breathing at 3.0 ATA are also shown. The steep fall in Po_2 on the arterial end of brain capillaries reflects the loss of oxygen from physical solution until capillary Po_2 falls to levels that are low enough to allow oxyhemoglobin dissociation. Overall, the data indicate that total brain oxygenation while breathing oxygen at 2.0 ATA is increased prominently by heavy exercise, with a calculated mean capillary Po_2 that approaches the level obtained at rest while breathing oxygen at 3.0 ATA.

In summary, under resting conditions, hyperventilation induced by breathing oxygen at increased pressures reduces arterial Pco_2. The associated reduction in brain blood flow provides a measure of protection against CNS oxygen toxicity by limiting the increase in brain oxygen dose. In contrast to oxygen-induced hyperventilation at rest, the ventilatory response to exercise is suppressed by hyperoxia. The associated progressive increments in arterial Pco_2 and brain blood flow increase total brain oxygenation and expose more brain cells to toxic Po_2 levels. This sequence of physiological responses provides a mechanism, at least in part, for the adverse effects of exercise on CNS oxygen tolerance.

Scientific and Operational Significance of Results

Results of experiments and new methods development summarized in this Final Report have established the following:

(a) Transcranial doppler measurements of middle cerebral arterial flow velocity provide a quantitative, reliable, noninvasive index of brain blood flow that can be measured on-line and continuously.

(b) Cerebral circulatory responses to increasing arterial Pco_2 during steady-state exercise have essentially the same slope as that observed at rest. Absolute values of brain blood flow during exercise are greater than resting values at fixed levels of arterial Pco_2, probably in response to an exercise-induced increase in arterial blood pressure.

(c) Development of an underwater work-measurement system and associated methods modifications permit the measurement of brain blood flow, ventilation, pulmonary gas exchange, arterial Po_2, Pco_2, and pH, cardiac rate, and arterial blood pressure in fully immersed subjects at rest and during exercise with accuracy and precision that are equivalent to that obtained under dry conditions.

(d) Ventilatory and brain blood flow responses to progressive hypercapnia at rest during head-out and total immersion do not differ significantly from corresponding responses to hypercapnia under dry conditions. These results do not support the hypothesis that physiological responses to immersion itself reduce central nervous system tolerance to oxygen poisoning.

(e) Ventilatory and brain blood flow responses to incremental exercise during head-out and total immersion do not differ significantly from corresponding responses to exercise under dry conditions. As above, these observations do not provide a physiological basis for the reported adverse influence of immersion on latency of oxygen convulsions.

(f) The previously observed prominent elevation of arterial Pco_2, with respect to resting values, during incremental exercise while breathing oxygen at 2.0 atmospheres (5) was confirmed in this Report. These observations were extended to provide quantitative measurements of previously predicted parallel changes in brain blood flow. The documented concurrent increments in arterial Pco_2 and brain blood flow remain the only known physiologic responses to hyperoxic exercise that should be expected to hasten oxygen convulsions by increasing brain oxygen flow and toxic oxygen dose.

(g) Therefore, it is rational to predict that concurrent decrements in arterial Pco_2, brain blood flow, and brain oxygen dose during light to moderate hyperoxic exercise can be achieved practically and effectively by sustaining a controlled degree of hyperventilation.

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FIG. 1

RELATIONSHIP OF ARTERIAL Pco_2 TO RATE OF CO_2 ELIMINATION DURING OXYGEN-EXERCISE EXPOSURE AT 2.0 ATA IN MAN

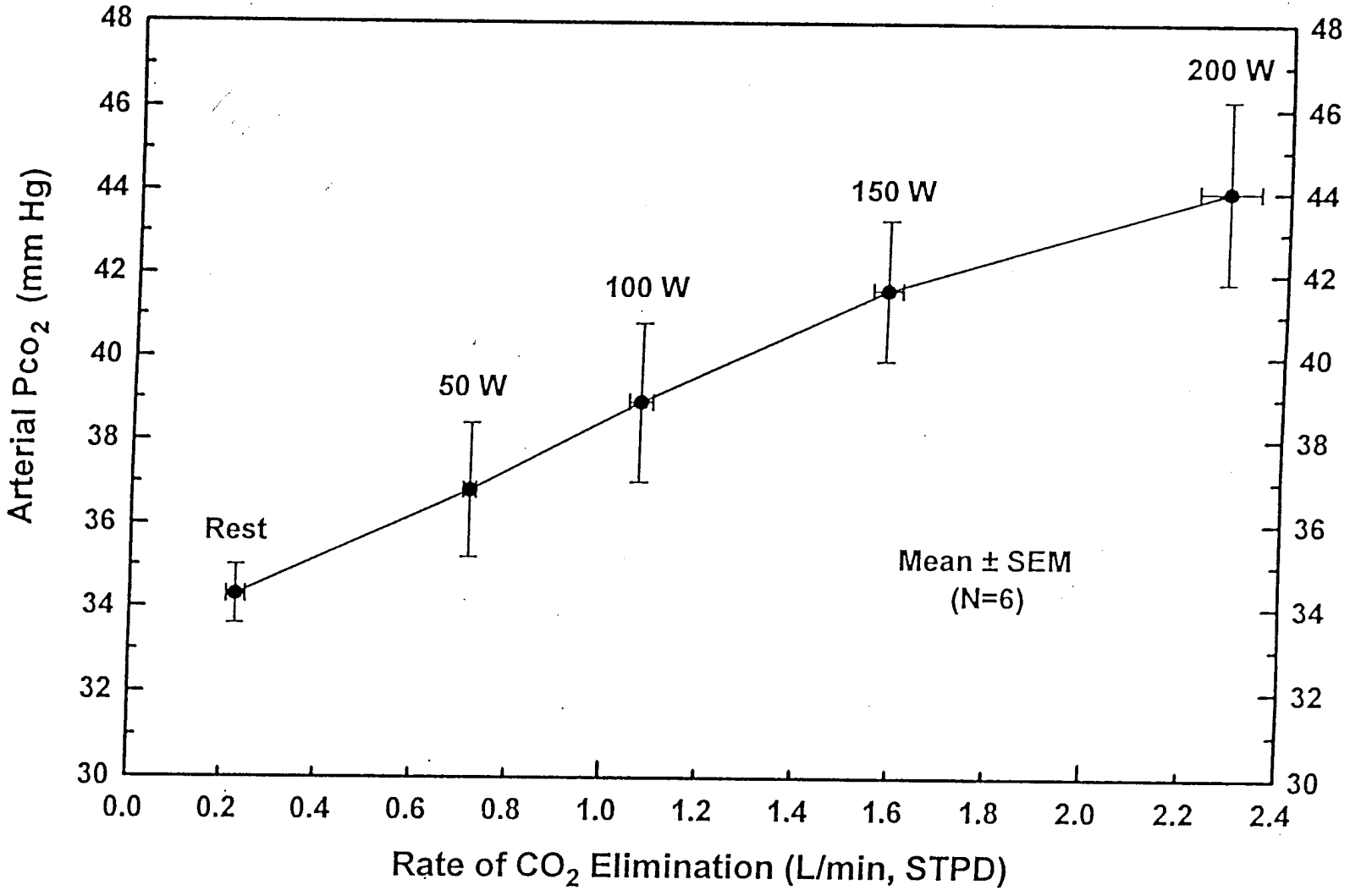

FIG. 2

COMPARISON OF EDU AND IFEM STUDIES OF EXERCISE EFFECTS ON CNS O_2 TOXICITY

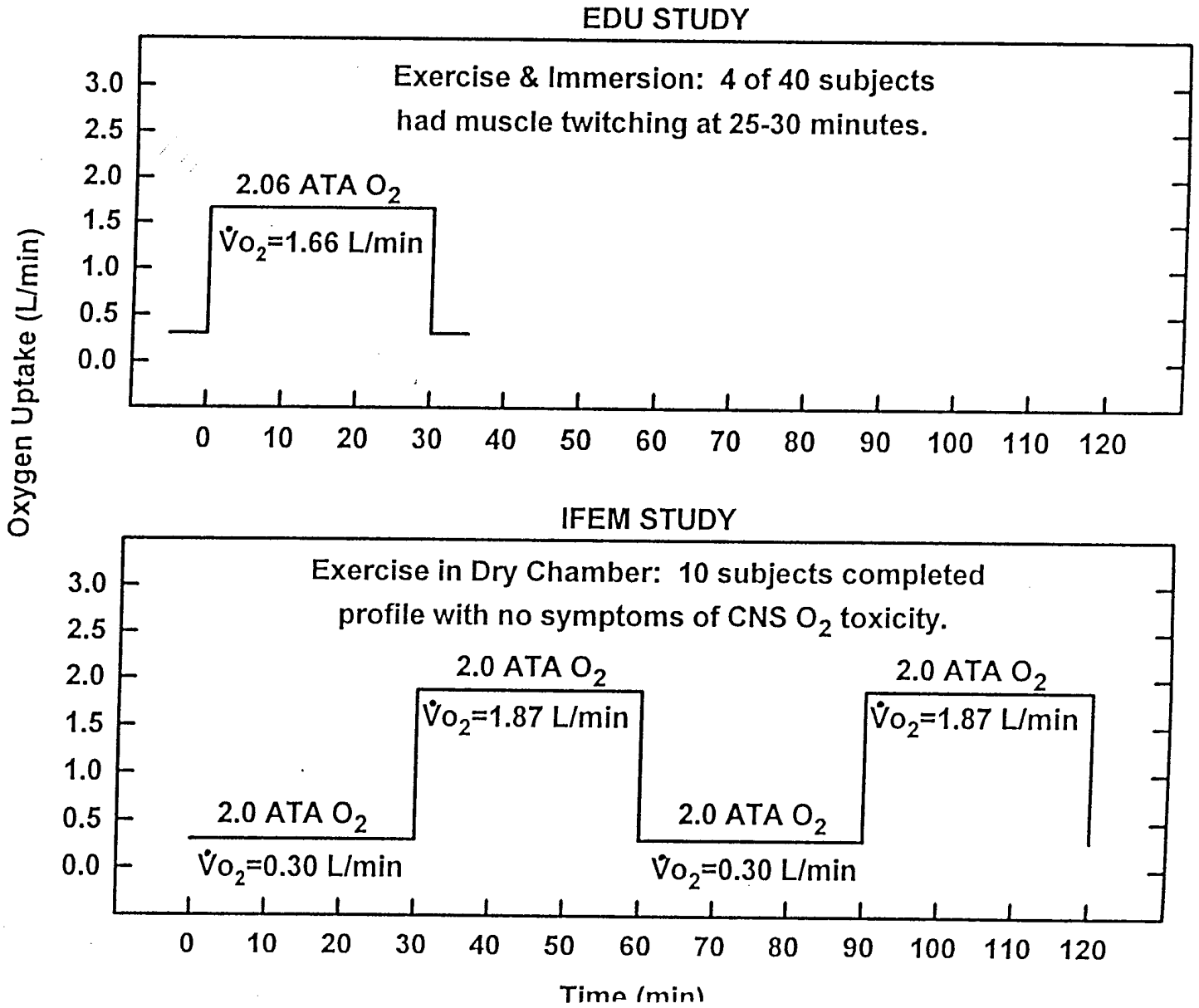

FIG. 3

PARABOLIC RELATIONSHIP OF CBF TO MCA BLOOD FLOW VELOCITY

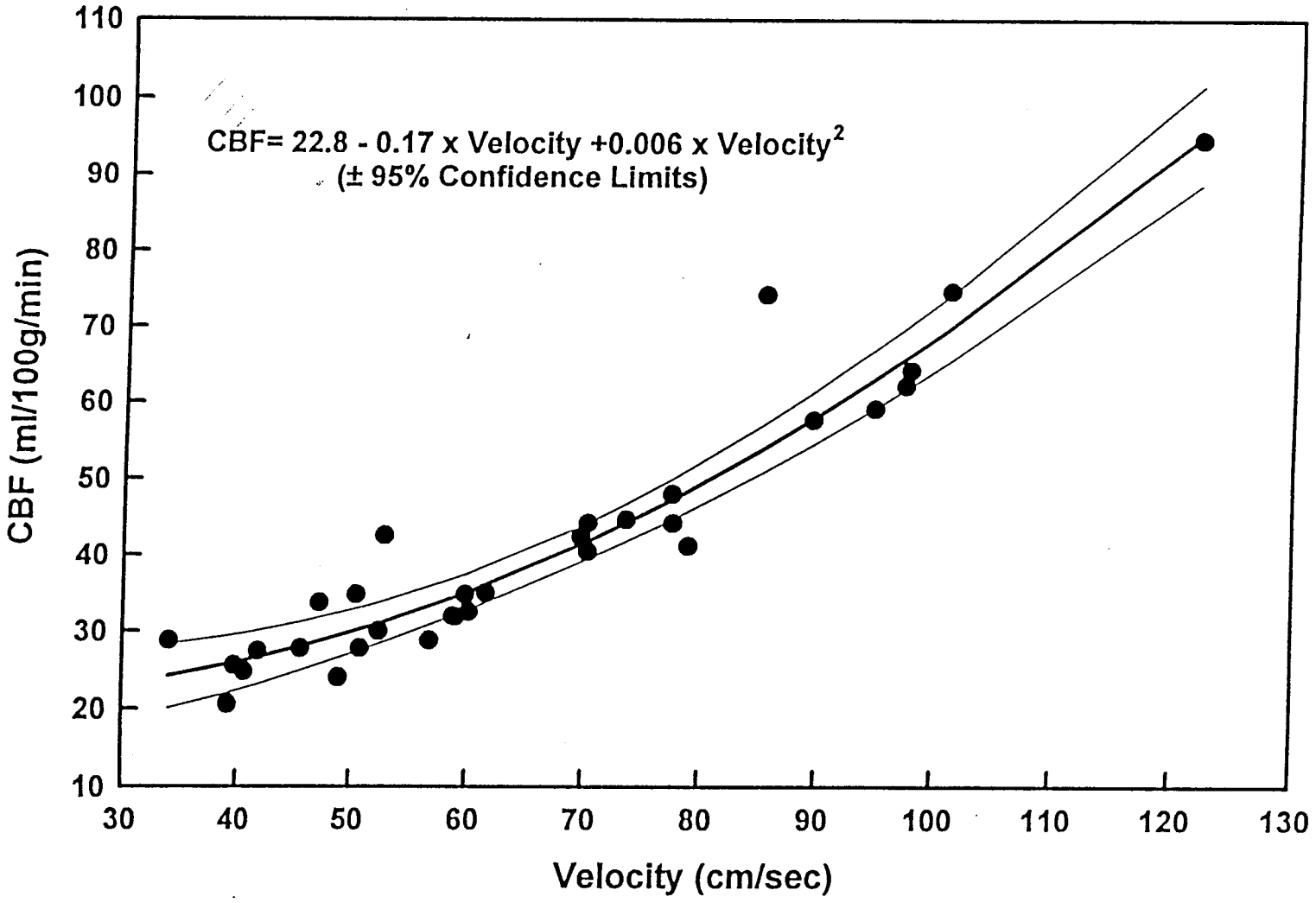

FIG. 4

LINEAR RELATIONSHIP OF PERCENT CBF CHANGE TO PERCENT BLOOD FLOW VELOCITY CHANGE

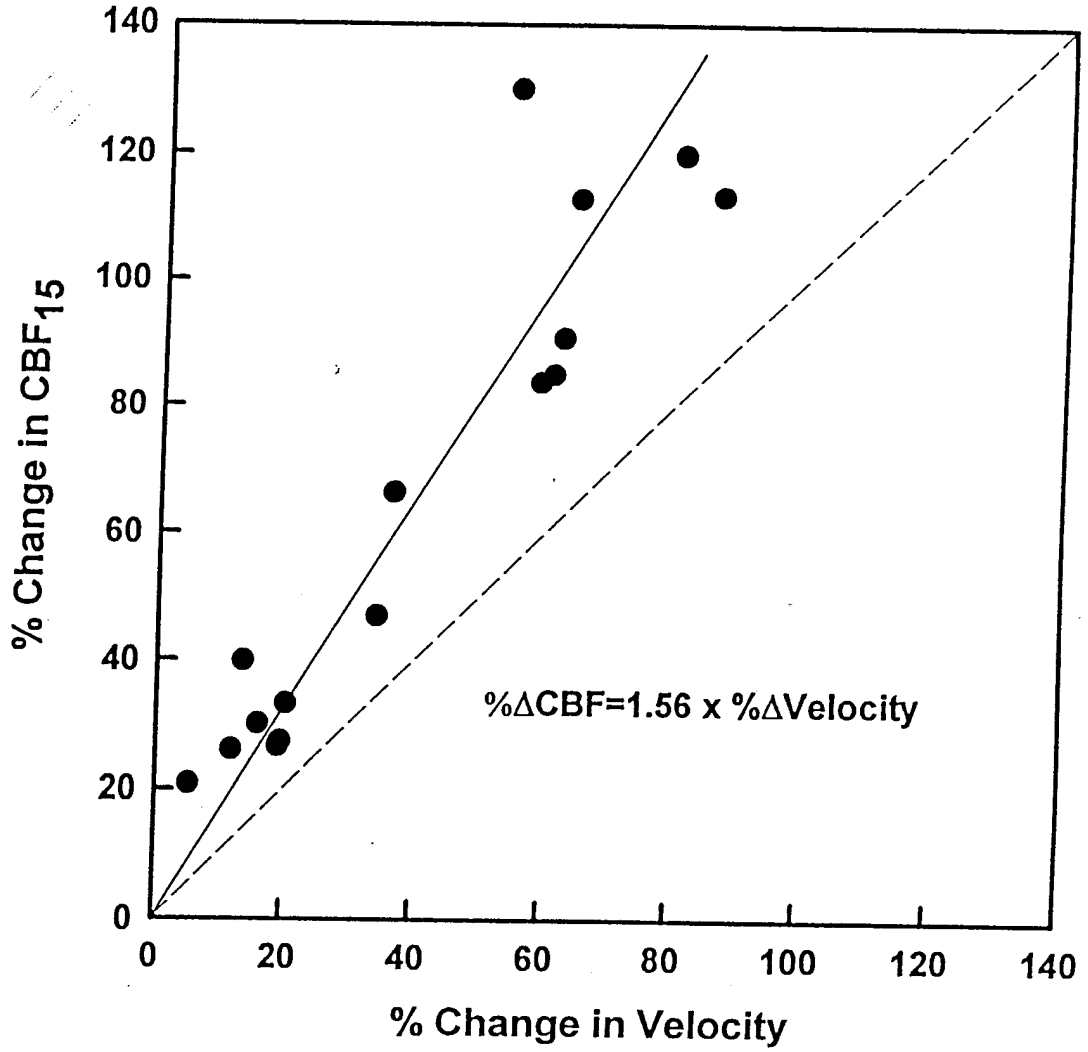

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FIG. 5

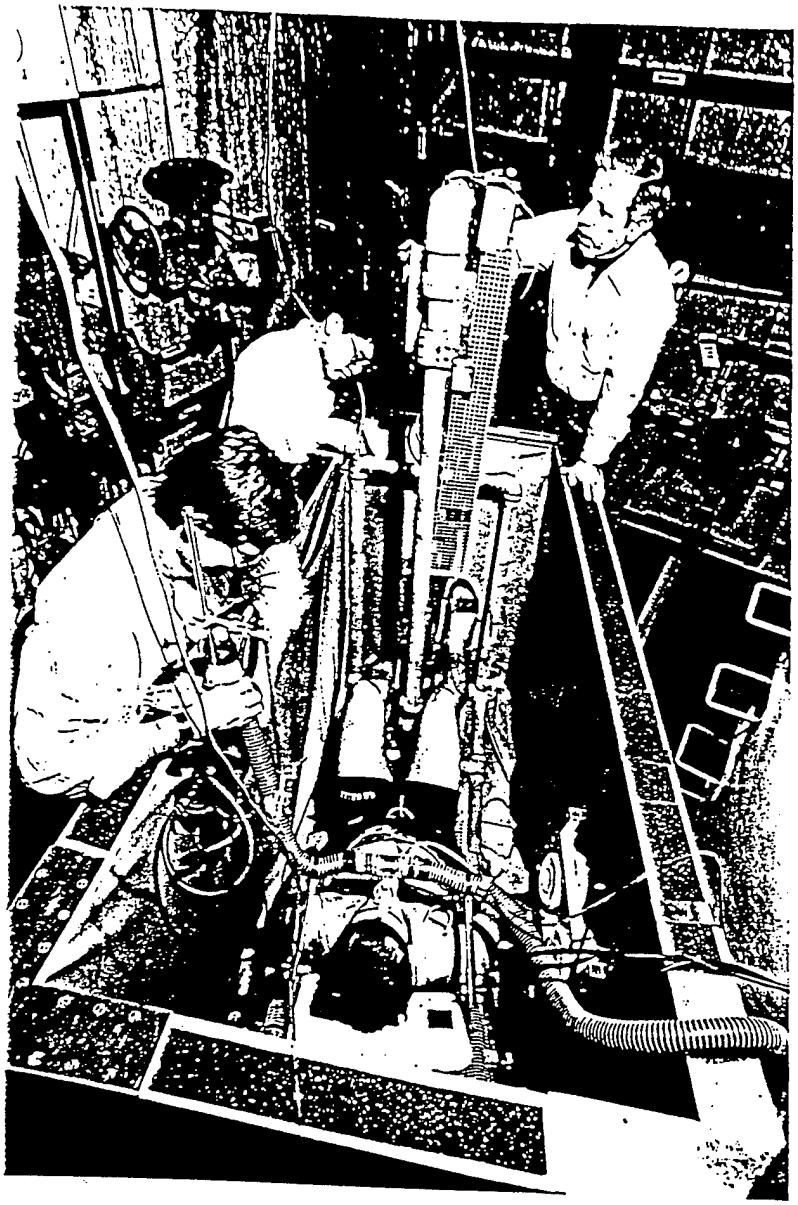

FIG. 6

RELATIONSHIPS OF O_2 UPTAKE TO ERGOMETER WORKLOAD UNDER WET AND DRY CONDITIONS

(Mean Values ± SEM, N=8, 60 RPM)

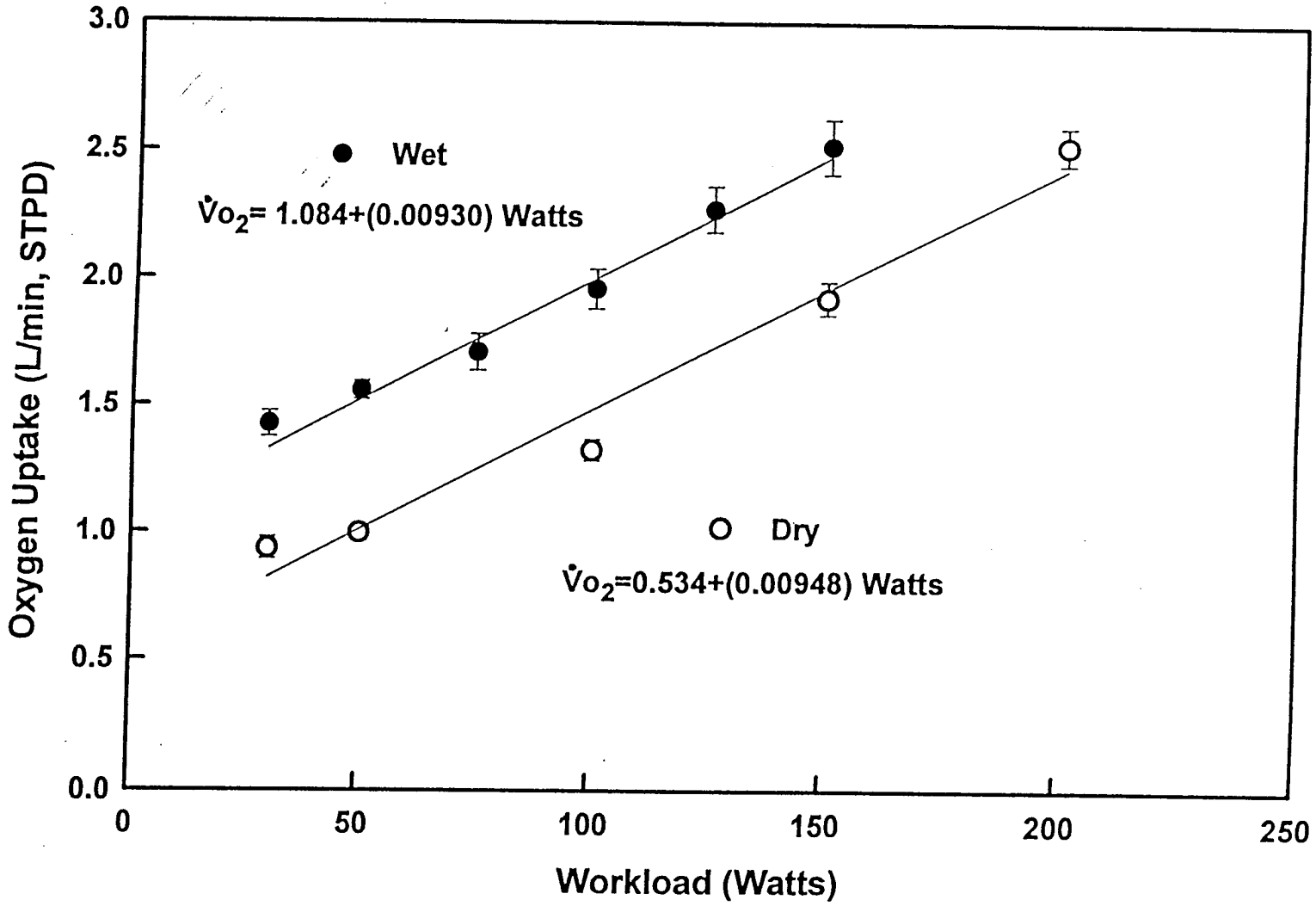

FIG. 7

EFFECT OF PEDALING RATE ON O_2 UPTAKE UNDER WET AND DRY CONDITIONS

(Mean Values ± SEM, N=8)

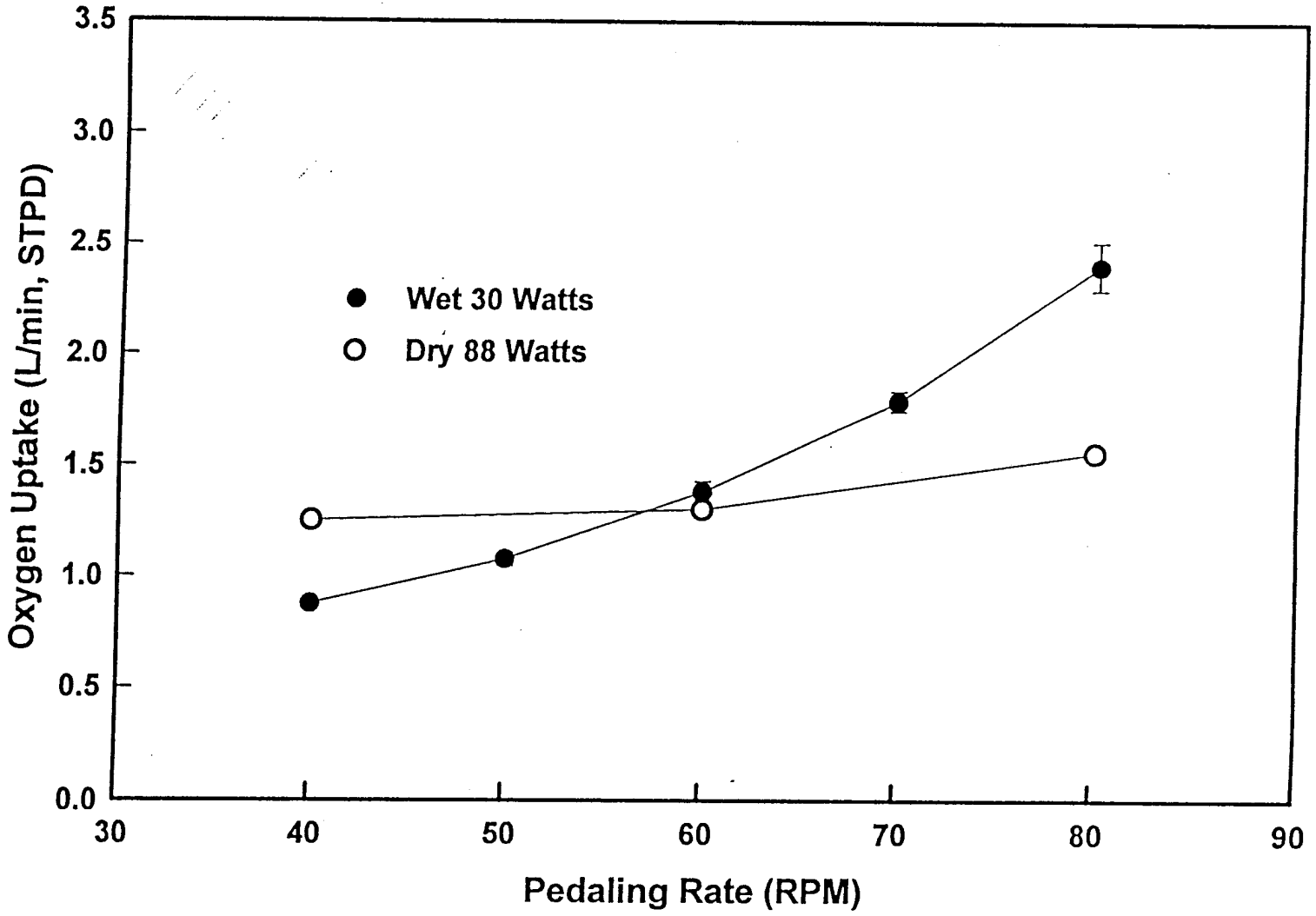

FIG. 8

VENTILATORY RESPONSES TO HYPERCAPNIA WHILE BREATHING OXYGEN AT REST AND DURING EXERCISE

(Mean Values ± SEM, N=7)

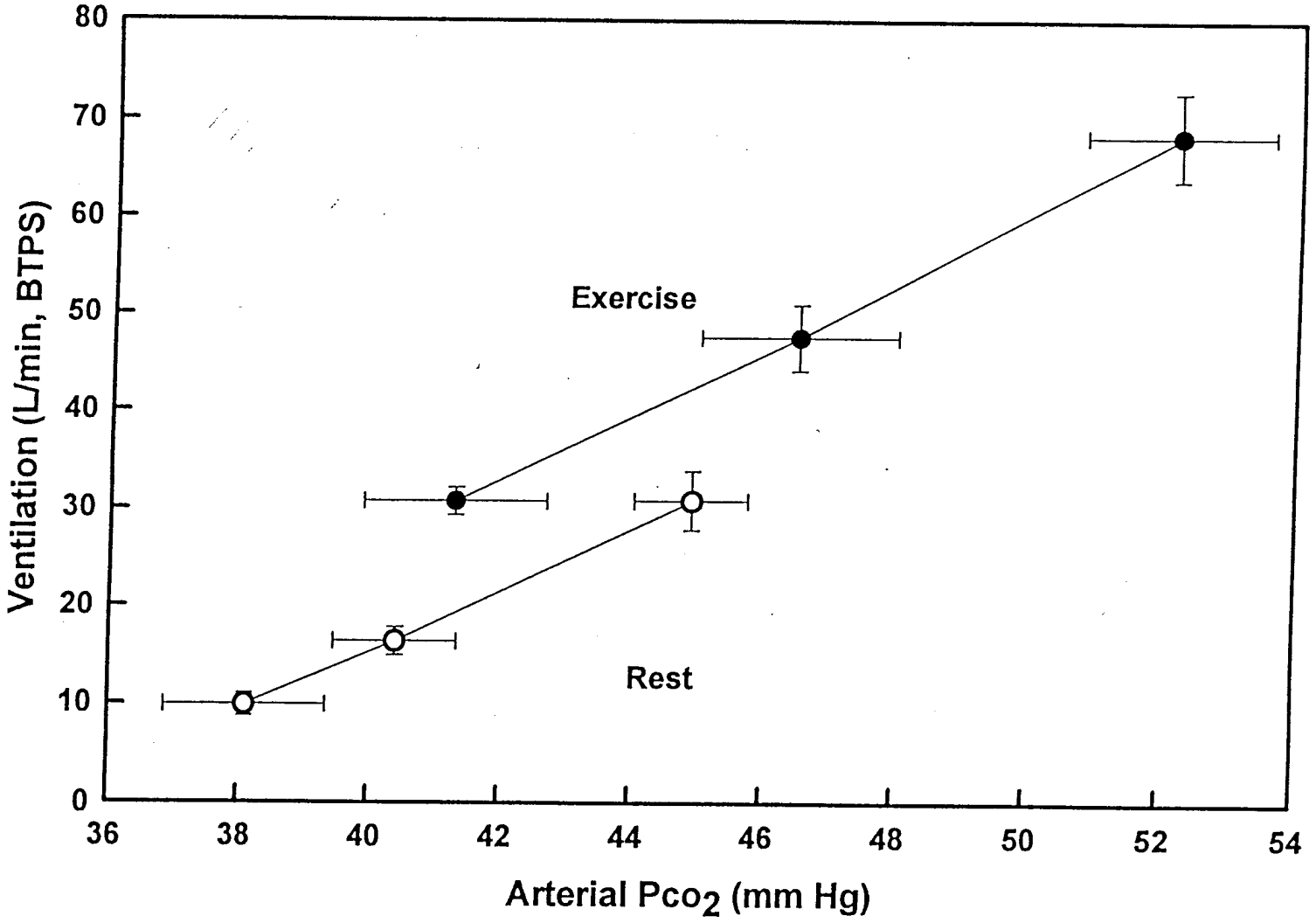

FIG. 9

RELATIONSHIPS OF MCA BLOOD FLOW VELOCITY TO ARTERIAL Pco_2 AT REST AND DURING EXERCISE

(Mean Values ± SEM, N=7)

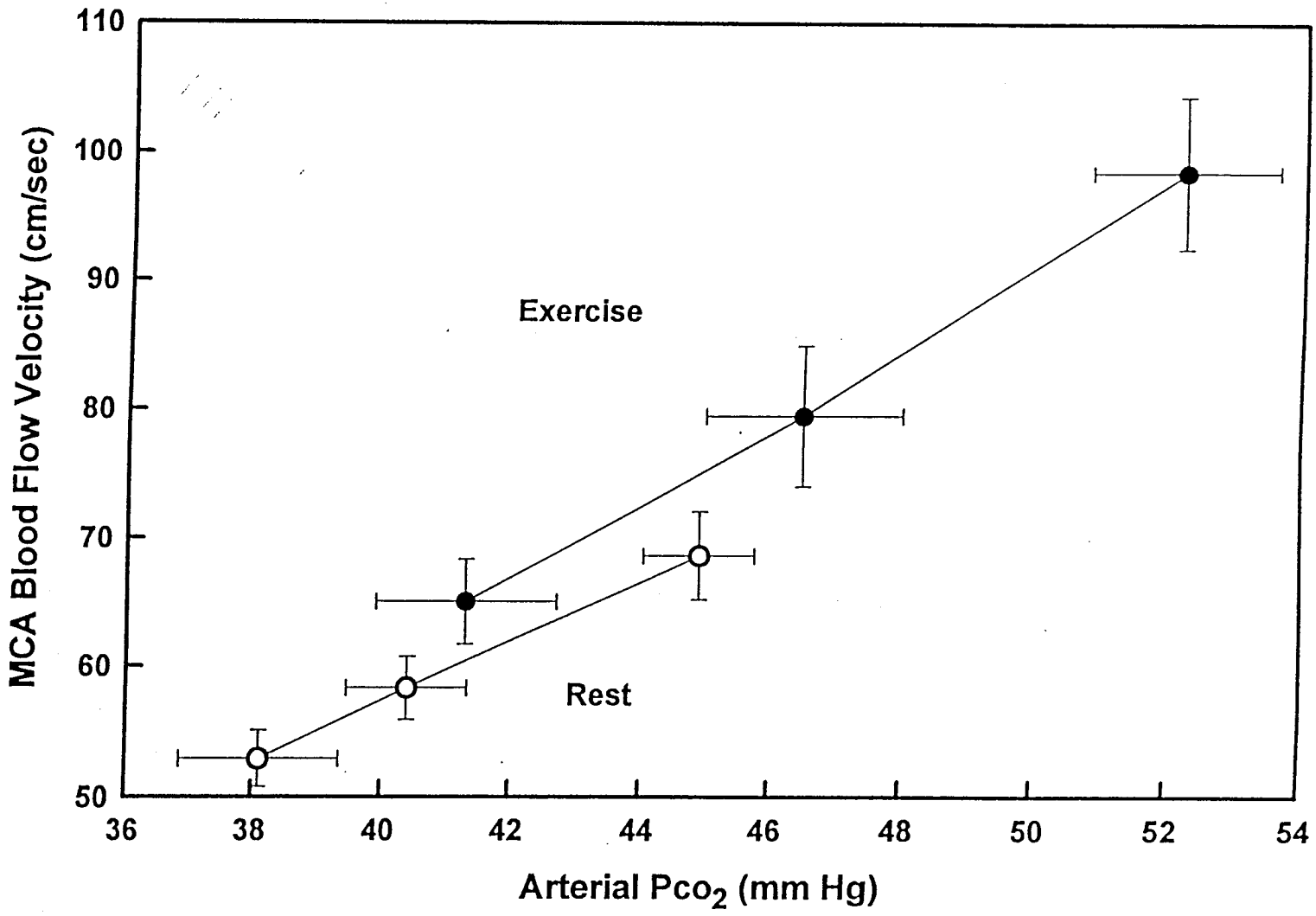

FIG. 10

EFFECTS OF HEAD-OUT AND TOTAL IMMERSION ON VENTILATORY RESPONSES TO HYPERCAPNIA

(Mean Values ± SEM, N = 8)

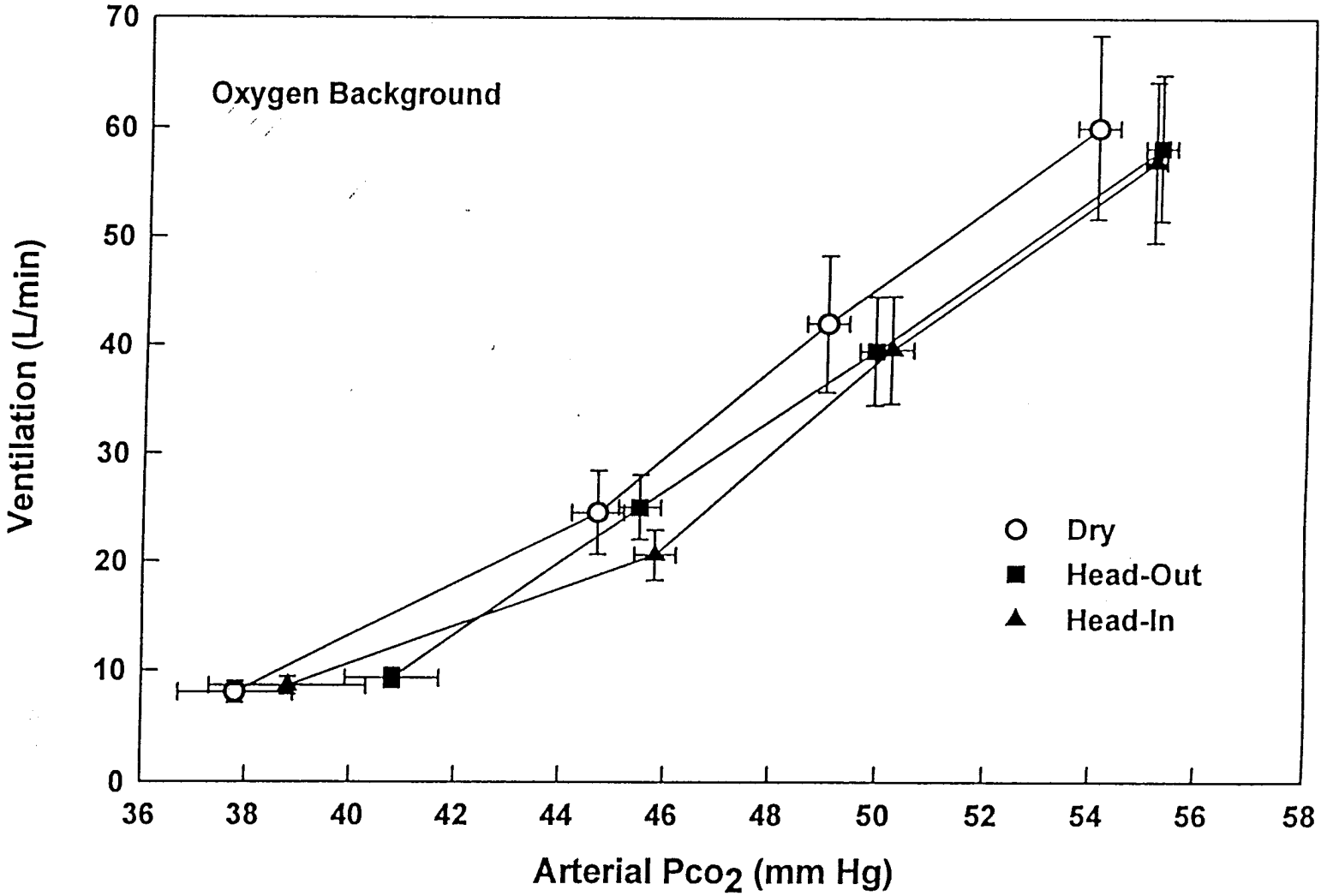

FIG. 11

EFFECTS OF HEAD-OUT AND TOTAL IMMERSION ON BODY TEMPERATURE RESPONSES TO HYPERCAPNIA

(Mean Values ± SEM, N = 8)

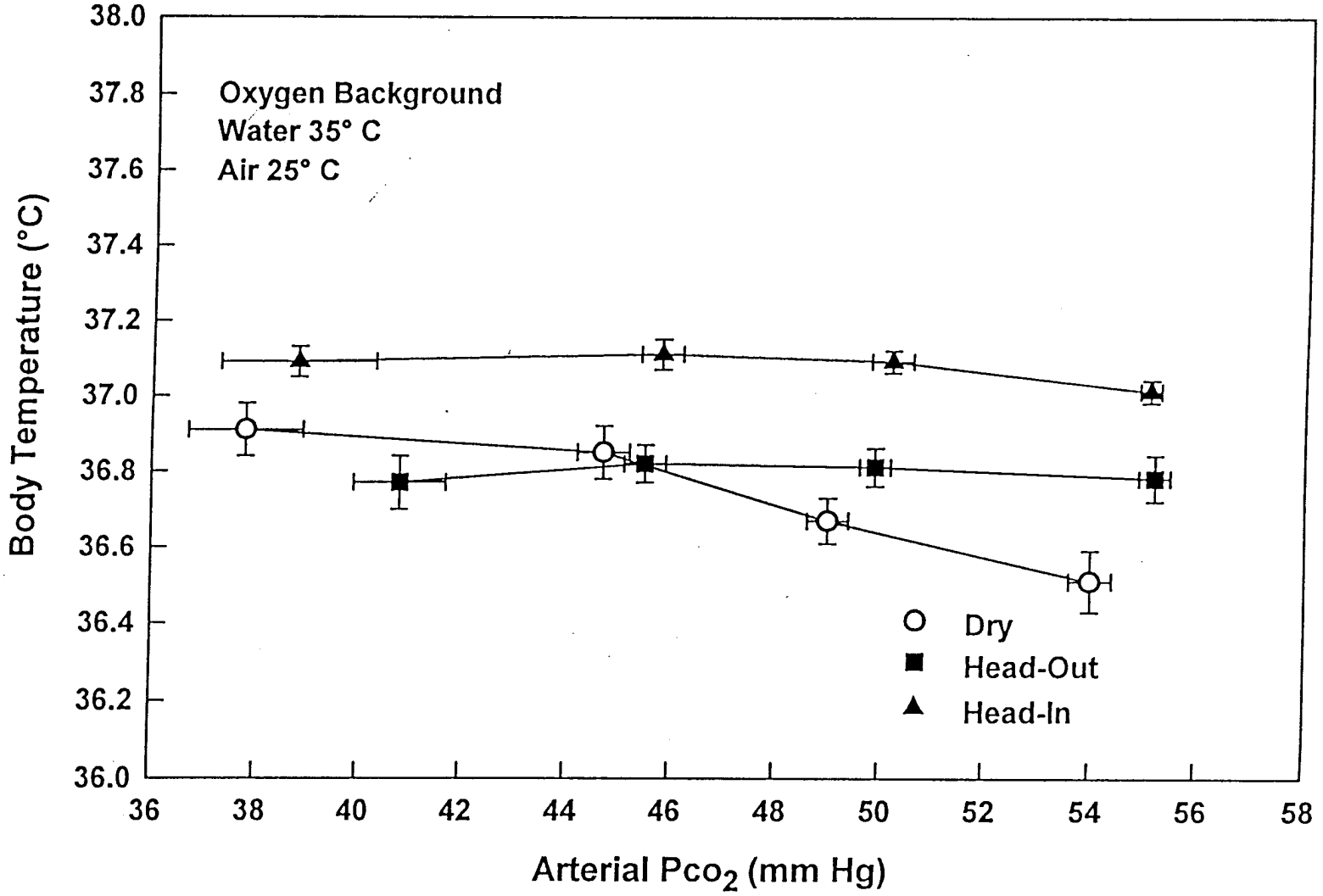

FIG. 12

EFFECTS OF HEAD-OUT AND TOTAL IMMERSION ON MEAN BLOOD PRESSURE RESPONSES TO HYPERCAPNIA

(Mean Values ± SEM, N = 8)

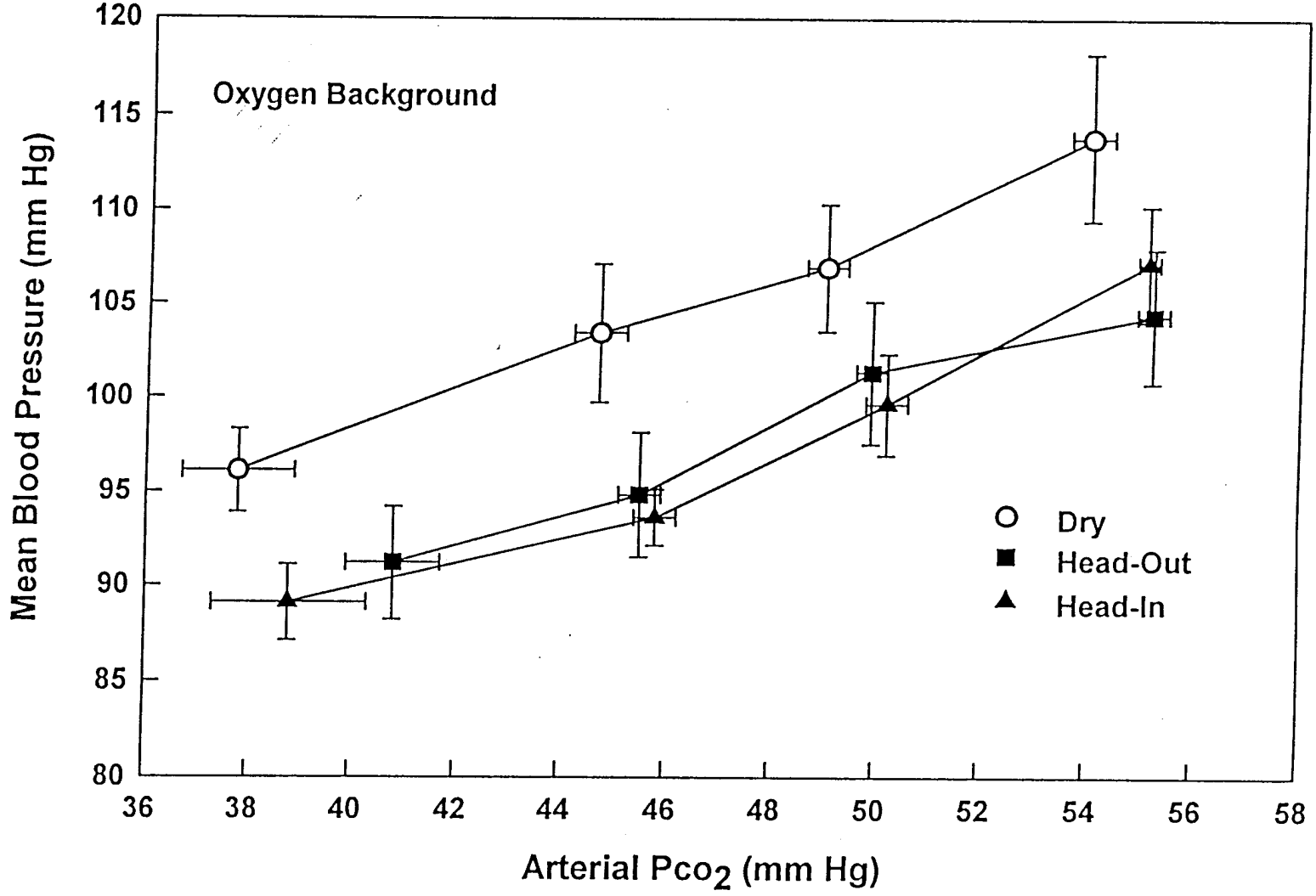

FIG. 13

EFFECTS OF HEAD-OUT AND TOTAL IMMERSION ON HEART RATE RESPONSES TO HYPERCAPNIA

(Mean Values ± SEM, N = 8)

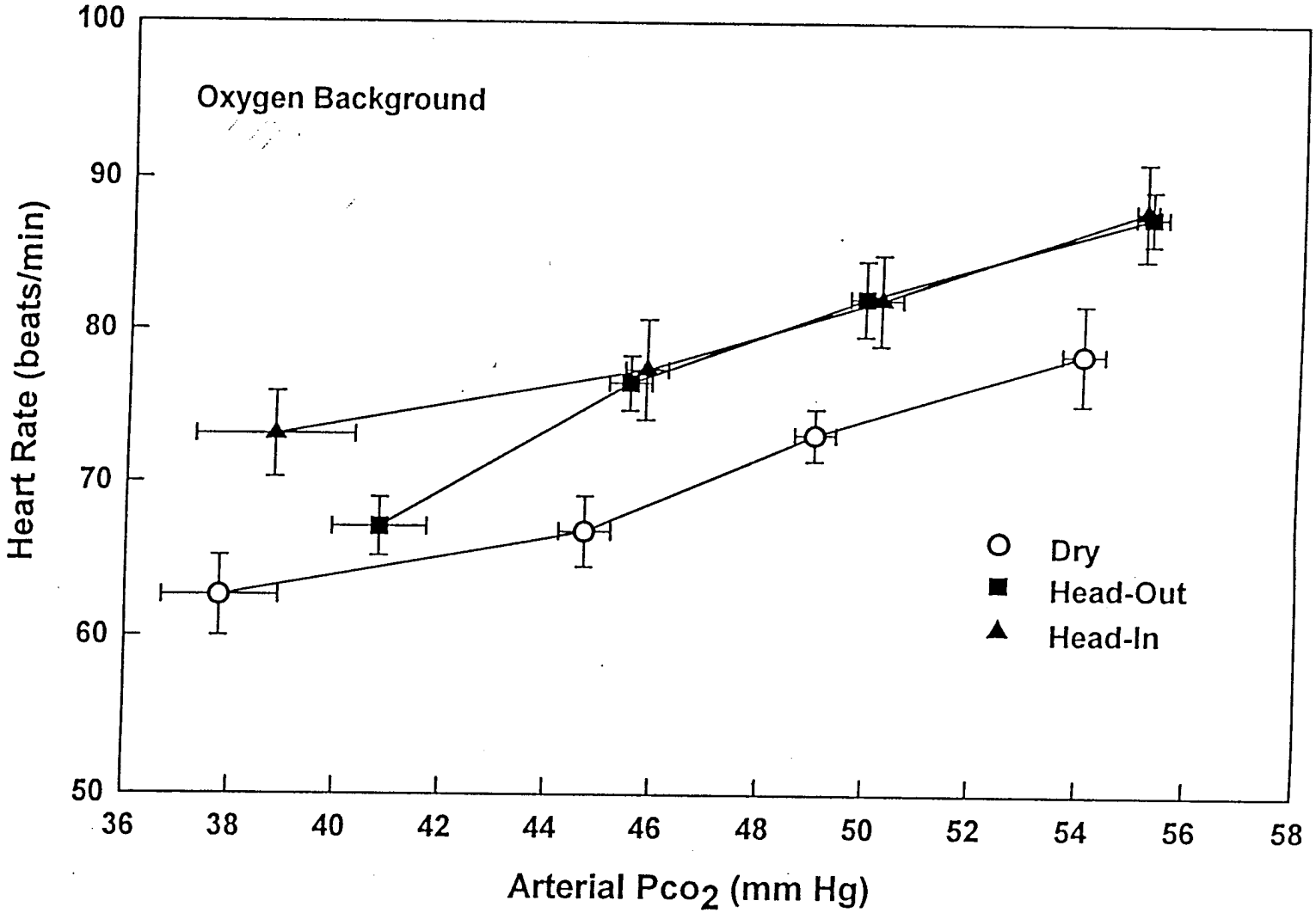

FIG. 14

EFFECTS OF HEAD-OUT AND TOTAL IMMERSION ON CEREBRAL CIRCULATORY RESPONSES TO HYPERCAPNIA

(Mean Values ± SEM, N = 8)

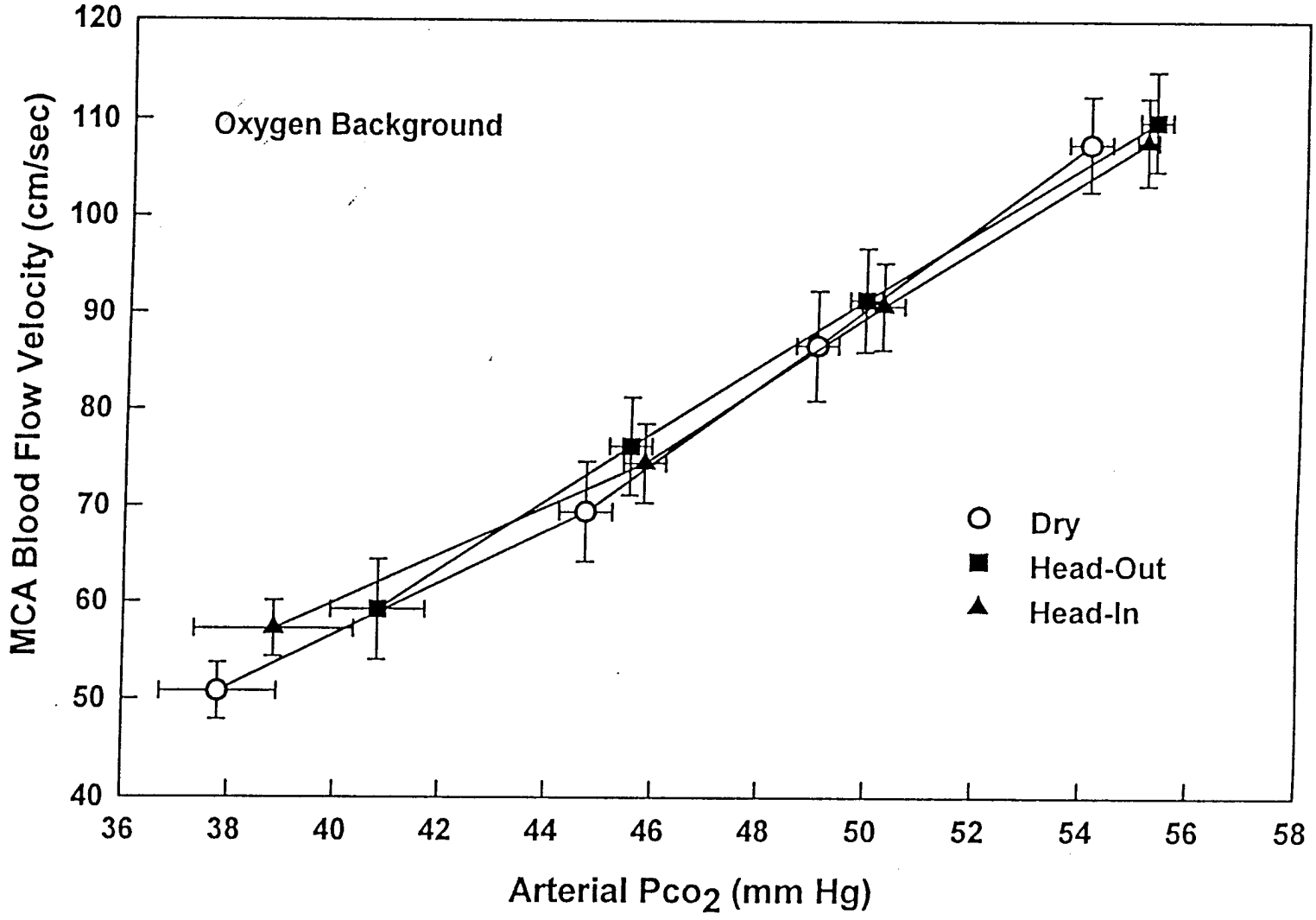

FIG. 15

EFFECTS OF HEAD-OUT AND TOTAL IMMERSION ON VENTILATORY RESPONSES TO EXERCISE

(Mean Values ± SEM, N = 8)

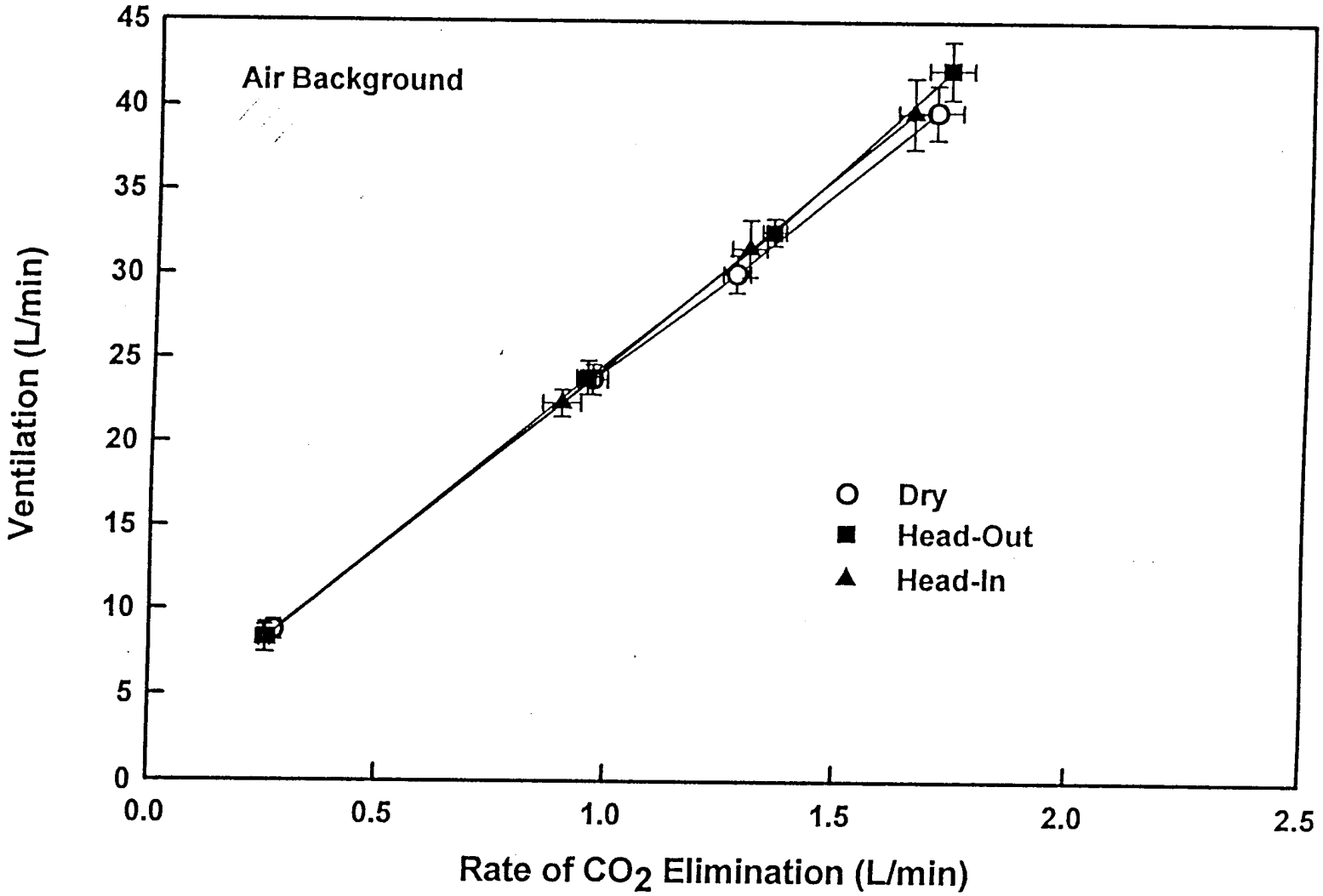

FIG. 16

EFFECTS OF HEAD-OUT AND TOTAL IMMERSION ON END-TIDAL Pco_2 RESPONSES TO EXERCISE

(Mean Values ± SEM, N = 8)

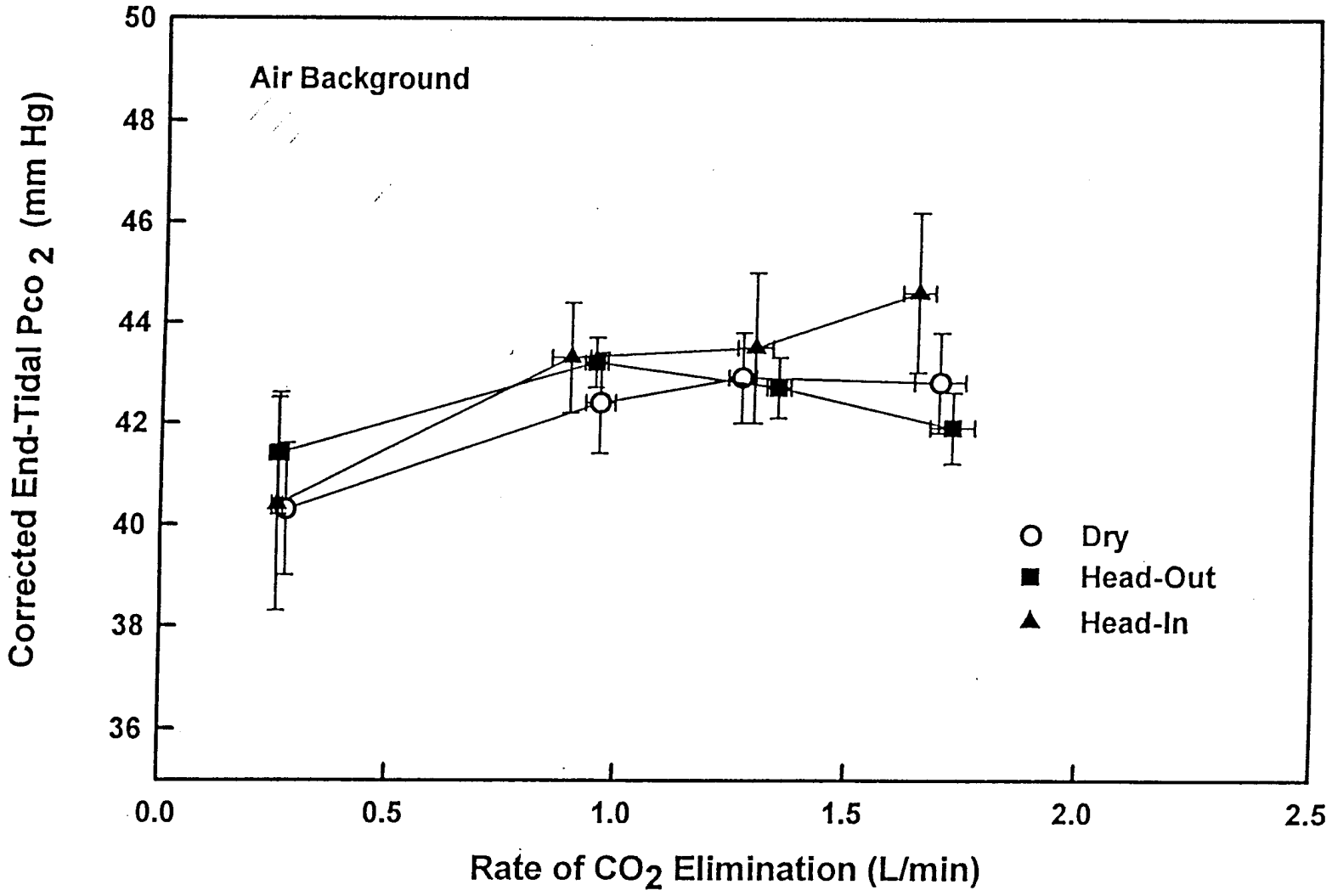

FIG. 17

EFFECTS OF HEAD-OUT AND TOTAL IMMERSION ON CERBERAL CIRCULATORY RESPONSES TO EXERCISE

(Mean Values ± SEM, N = 8)

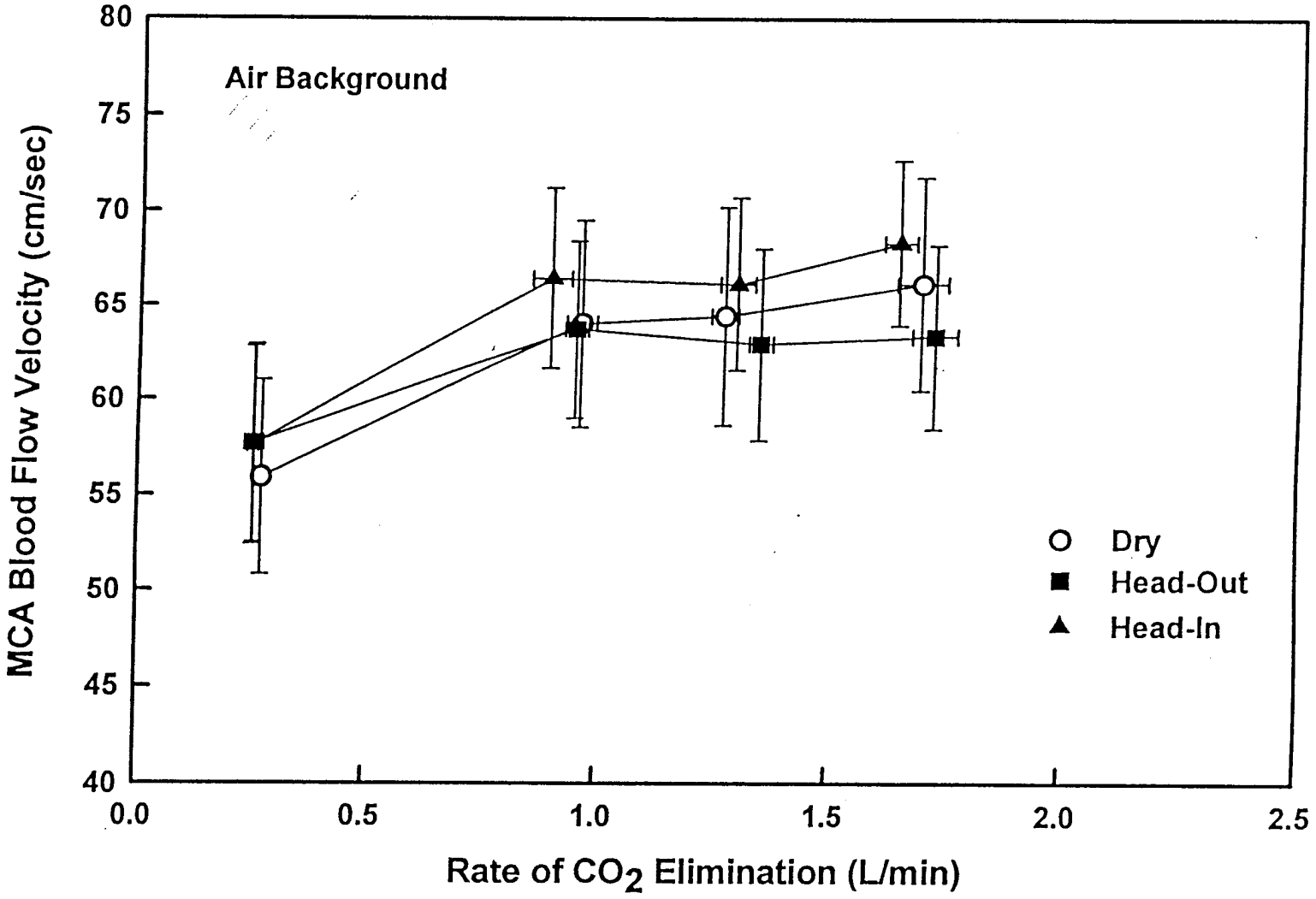

FIG. 18

EFFECTS OF INCREASED GAS DENSITY AND OXYGEN AT 2.0 ATA ON VENTILATORY RESPONSES TO INCREMENTAL EXERCISE

(Mean Values ± SEM in 9 Men)

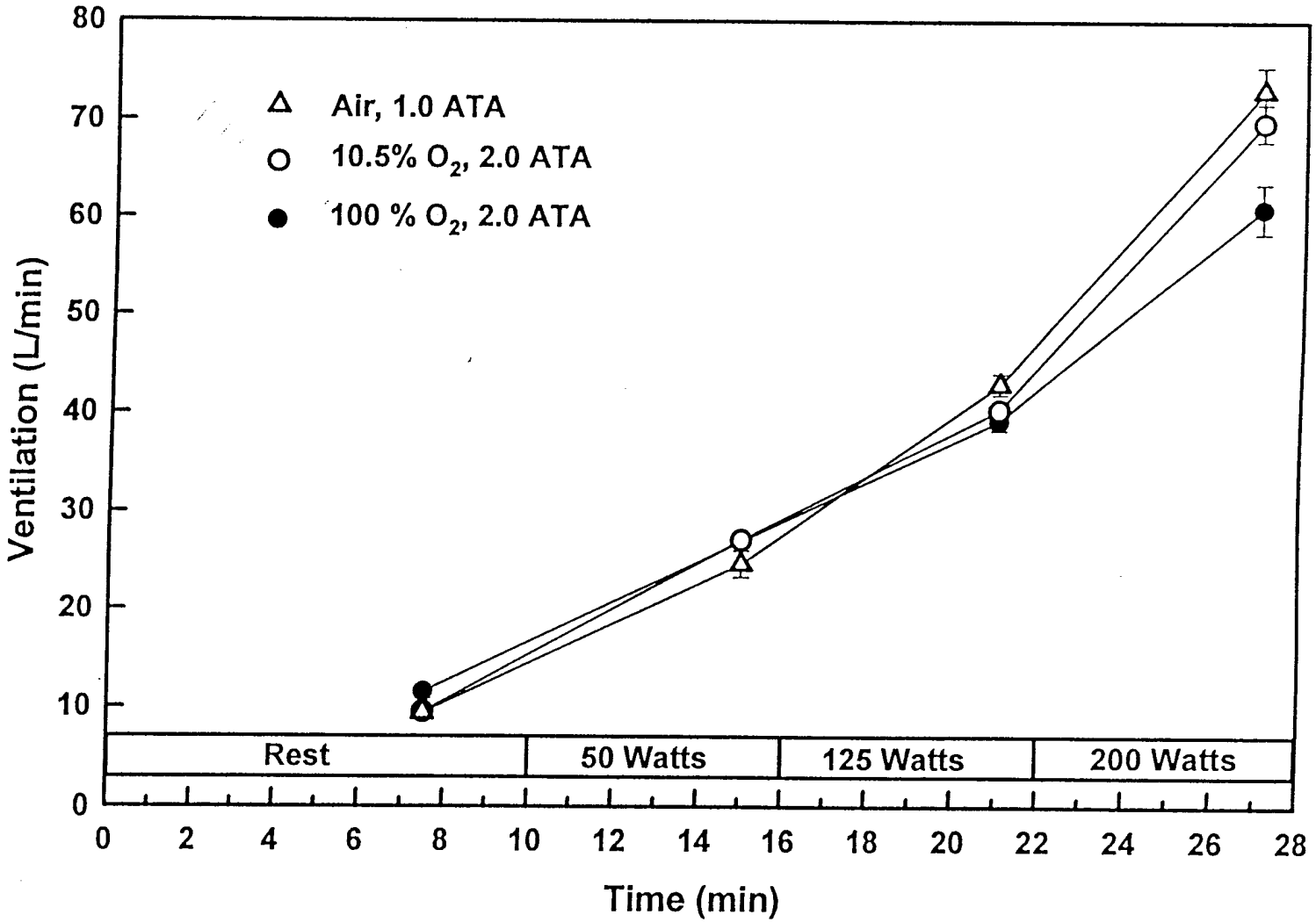

FIG. 19

EFFECTS OF INCREASED GAS DENSITY AND OXYGEN AT 2.0 ATA ON ARTERIAL Pco_2 RESPONSES TO INCREMENTAL EXERCISE

(Mean Values ± SEM In 9 Men)

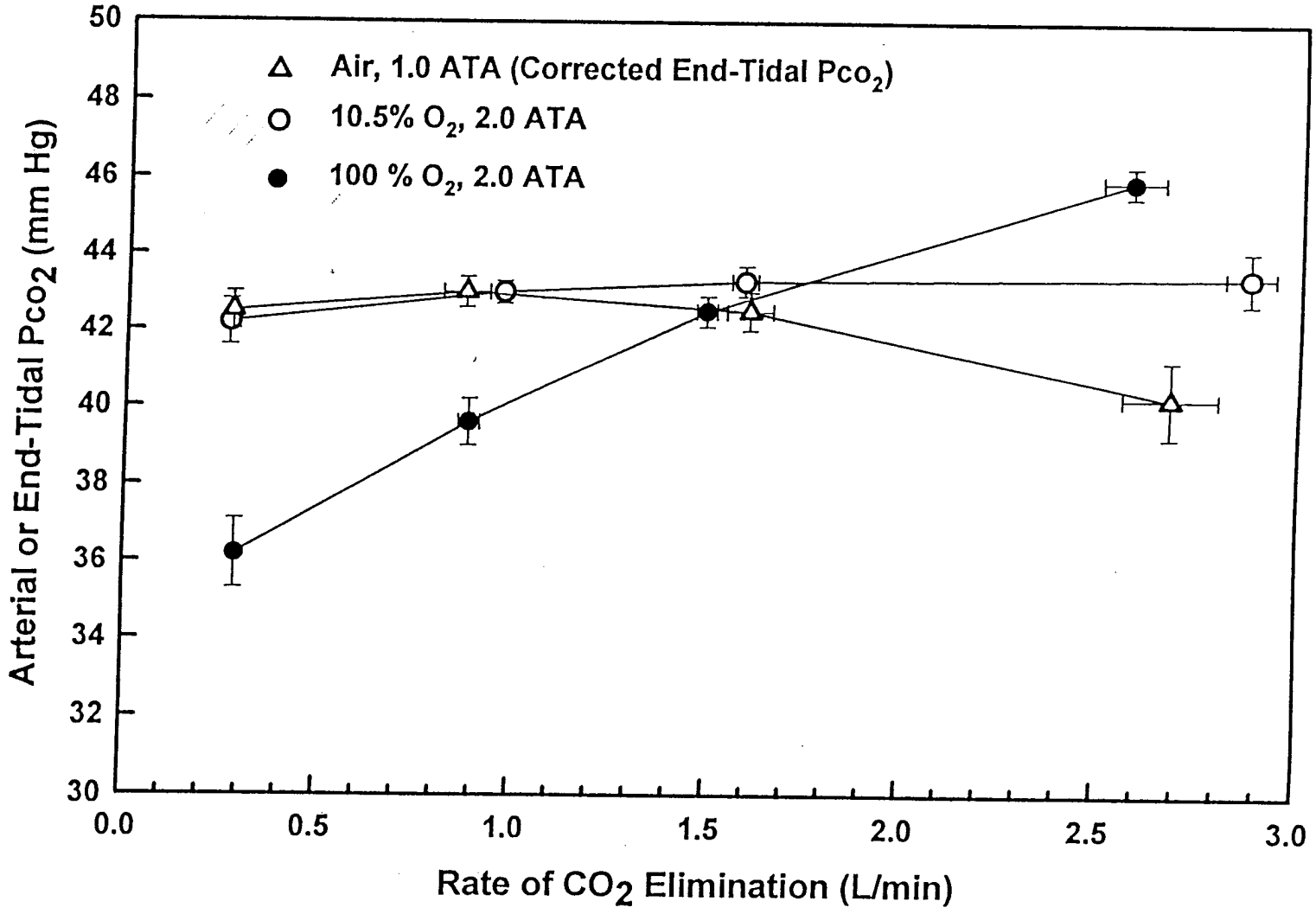

FIG. 20

EFFECTS OF INCREASED GAS DENSITY AND OXYGEN AT 2.0 ATA ON CEREBRAL CIRCULATORY RESPONSES TO INCREMENTAL EXERCISE

(Mean Values ± SEM In 9 Men)

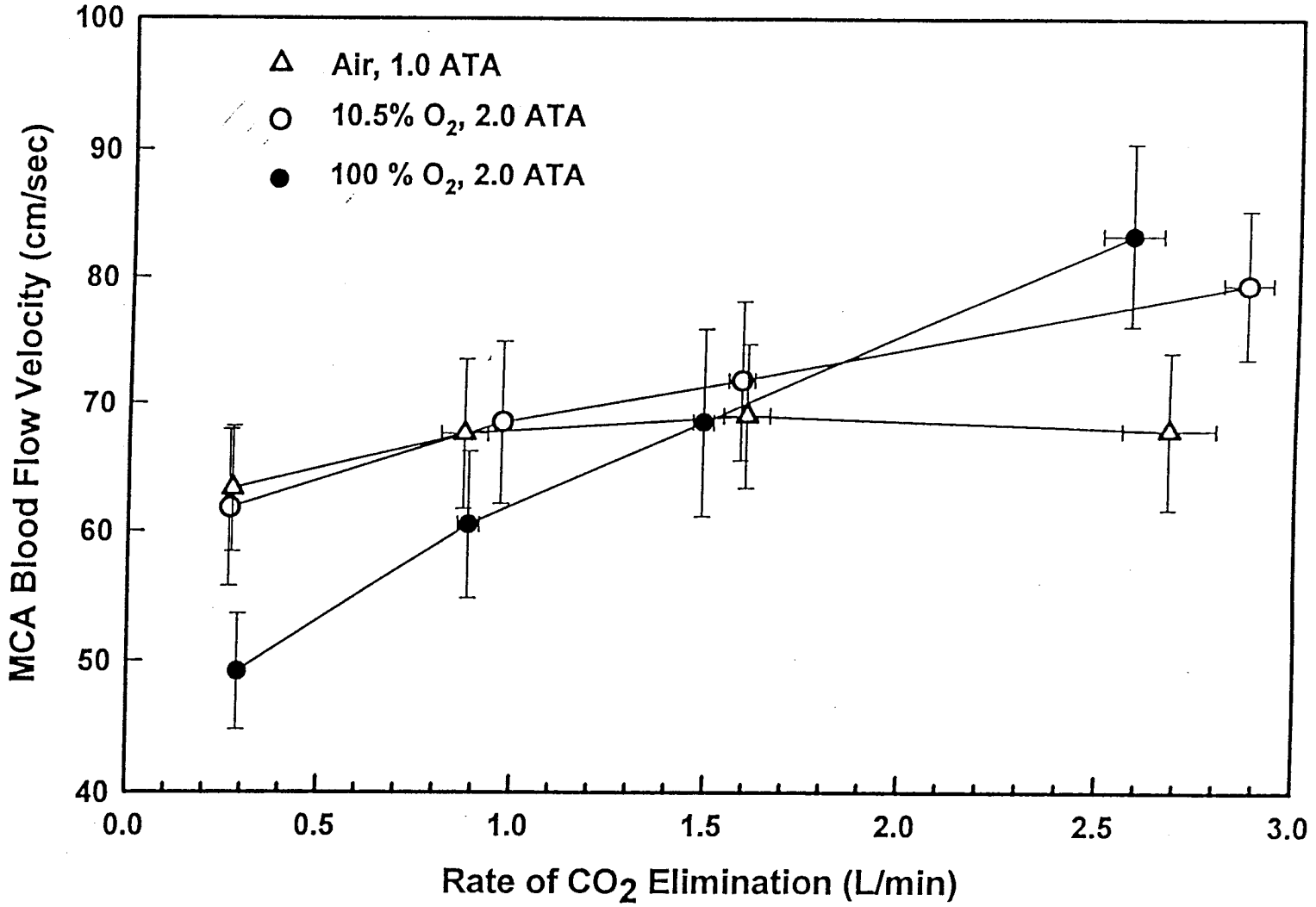

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FIG. 21

BRAIN VENOUS AND MEAN CAPILLARY Po_2 RESPONSES TO INCREMENTAL EXERCISE WHILE BREATHING 10.5% AND 100% O_2 AT 2.0 ATA

(Mean Values in 8 Men)

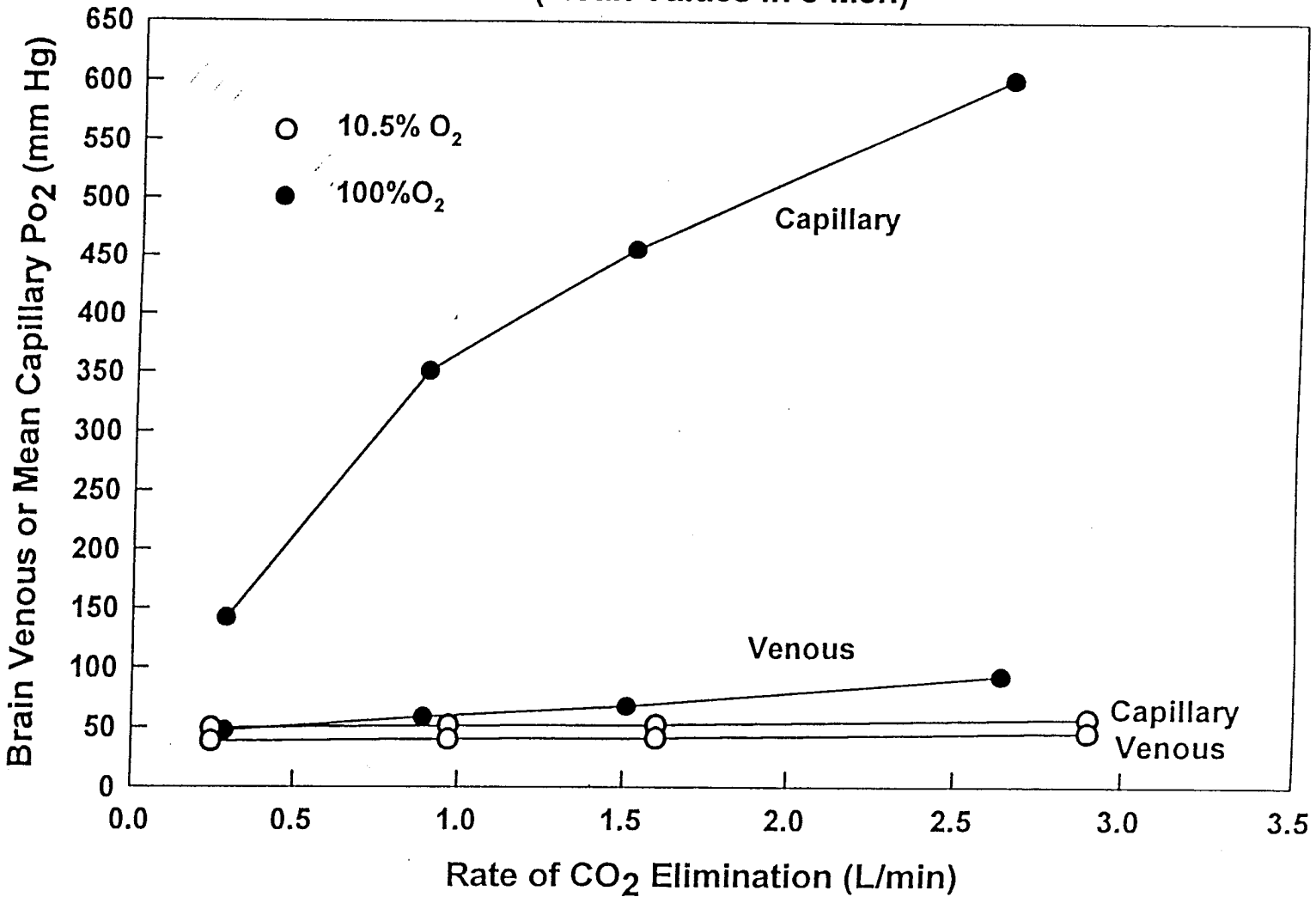
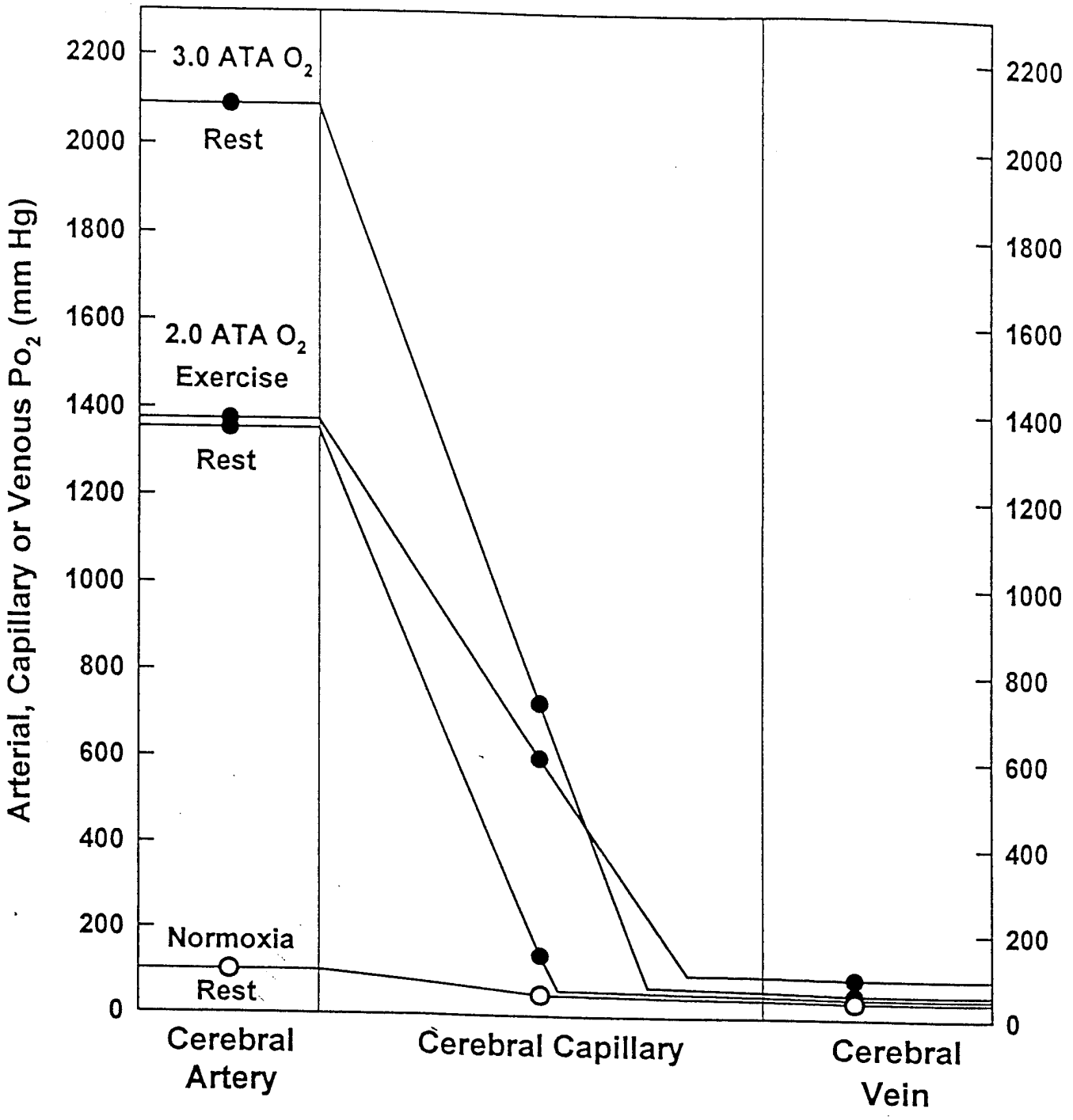


FIG. 22

EFFECTS OF HYPEROXIA ON BRAIN OXYGENATON AT REST AND DURING EXERCISE



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Human Tolerance and Physiological Responses to Exercise While Breathing Oxygen at 2.0 ATA

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G. BECK, JR., B.S., and D. G. FISHER, B.S.

CLARK JM, GELFAND R, LAMBERTSEN CJ, STEVENS WC, BECK G JR., FISHER DG. *Human tolerance and physiological responses to exercise while breathing oxygen at 2.0 ATA.* Aviat. Space Environ. Med. 1995; 66:336–45.

Multiple physiological functions were monitored in ten men who performed two 30-min periods of 150-W ergometer exercise during 120-min exposures to O_2 at 2.0 ATA. There were no convulsions or electroencephalographic manifestations of increased excitability. Sequential measurements of peripheral visual fields, pulmonary mechanical function, mental performance, and cardiovascular function during the resting recovery after each of the two exercise periods were not detectably altered from pre-exercise control values. Pre- and post-exposure measurements of visual acuity, accommodation, pupil diameter, visual cortical activity, and retinal electrical activity also revealed no significant differences. While CNS symptoms were absent, average arterial Pco_2 rose by about 5 mm Hg during both exercise periods. This finding was confirmed in six subjects who performed four 6-min periods of continuous exercise at 50, 100, 150, and 200 W while breathing O_2 at 2.0 ATA. Average arterial Pco_2 rose nearly linearly from 34.3 mm Hg at rest to 44.0 mm Hg at 200 W. Arterial Pco_2-related increments in brain blood flow and Po_2 may explain part or all of the known detrimental influence of exercise on CNS O_2 tolerance.

ADVERSE EFFECTS of exercise on central nervous system (CNS) O_2 tolerance in man are well known and have been demonstrated repeatedly in working divers (3,4,11,24,29). These effects are manifested most prominently by the occurrence of O_2 convulsions at shorter exposure times or at lower O_2 pressures than those found in men at rest. The characteristics of O_2 convulsions and the premonitory symptoms or signs that may occur before the convulsion begins have been described (17). Although the development of CNS O_2 toxicity may be accelerated in all individuals by effects of concurrent exercise, there are indications that some men are unusually susceptible to the occurrence of O_2 convulsions during exercise (3,4). The causes of this phenomenon are not known, and susceptible individuals still cannot be identified in advance.

Most previous studies of exercise effects on CNS O_2 tolerance have focused on occurrence of signs and symptoms with little emphasis on objective physiological measurements (3,4,11,29). Oxygen-exercise interactions may be associated with measurable changes that provide clues regarding possible causes of accelerated convulsions, or some means to identify unusually susceptible individuals. This study was designed to investigate such possibilities by making objective measurements of CNS responses to oxygen-exercise exposure in a dry chamber at 2.0 ATA, along with concurrent measurements of ventilatory, temperature, pulmonary, and cardiac responses that were found in Predictive Studies V to be altered during earlier, continuous hyperoxic exposures of men at rest (7,13,18,26). The present paper is the first of an ongoing series of studies (Predictive Studies VII) that are designed to evaluate effects of exercise on O_2 tolerance in man.

The initial experiment design involved breathing O_2 at 2.0 ATA while two 30-min, steady-state work periods were alternated with 30-min rest/measurement periods. Although no effects of CNS O_2 toxicity were found, arterial Pco_2 was consistently elevated during the periods of exercise. Even in the absence of symptoms, this response to exercise while breathing O_2 is relevant to the development of CNS O_2 poisoning by virtue of its known influence on brain blood flow and O_2 dose (16,17,19,27). Accordingly, the original experiment design was expanded by obtaining additional measurements of arterial Pco_2 as subjects performed four con-

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secutive 6-min periods of incremental exercise while breathing O_2 at 2.0 ATA. Arterial P_{CO_2} rose progressively in proportion to the level of exercise. Results of the arterial P_{CO_2} measurements and their potential significance are reported below, along with the results of other relevant measurements that were not altered by the oxygen-exercise exposures at 2.0 ATA.

METHODS

The two selected exercise profiles were performed inside a dry compression chamber large enough to accommodate the subject, bicycle ergometer (Pedalmate, W. E. Collins, Inc., Braintree, MA), two investigators, and required instrumentation. Additional details describing the chamber system are available (20).

Ergometer exercise was performed with the subject reclining on a padded ambulance gurney. The gurney backrest was elevated sufficiently to provide a firm support against which the subject could brace while pedalling the ergometer. The partially elevated backrest also provided a padded support against which the subject could be restrained if a convulsion occurred.

Subjects

Each of the 10 male subjects received a comprehensive medical evaluation which included a medical history and physical examination, neuro-ophthalmologic evaluation, electrocardiogram, electroencephalogram, electroretinogram, visual acuity and fields, chest x-ray, urinalysis, and hematology profile. No women were studied because there were no female volunteers. Informed consent was obtained on two separate occasions prior to oxygen-exercise exposure at 2.0 ATA. The experiment protocol was reviewed and approved by the Human Studies Committee of the University of Pennsylvania.

The fitness level of each subject was evaluated preexposure by measuring ventilatory and gas exchange responses to graded exercise on the bicycle ergometer in two separate trials. Average maximum oxygen uptake in the supine position for all 10 subjects was 4.18 $L \cdot min^{-1}$ or 50 $ml \cdot kg^{-1} \cdot min^{-1}$ at an average ergometer workload of 245 W.

Gas Administration System

Oxygen from a liquid source was humidified to 80% relative humidity and delivered to a 30-L storage bag. Inspired O_2 from the bag was conducted via 1.5-inch i.d. tubing to an exercise test mask (Cat. #7900M, Hans Rudolph, Inc., Kansas City, MO) with rated inspiratory and expiratory pressure changes at 600 $L \cdot min^{-1}$ of 6.2 and 4.8 cm H_2O, respectively. Expired gas was conducted via 1.5-inch i.d. tubing to an overboard dump system and expelled from the chamber or collected in a weather balloon for respiratory measurements.

Exercise Profiles

Alternating rest and exercise (Study I): An individual workload equivalent to about 60% of his average maximal value was selected for each subject. The average ergometer workload for the ten subjects who performed the alternating rest and exercise profile was 150 W (range 125–160). When sustained over two 30-min periods which were separated by 30 min of rest, this workload represented prominent exercise stress that could be performed only by fit individuals.

The alternating rest and exercise profile was performed by each subject during air breathing at 1.0 ATA on a day prior to performing the same profile during O_2 breathing at 2.0 ATA. The 120-min O_2 exposure consisted of two 30-min exercise periods preceded and separated by 30-min rest/measurement periods (Fig. 1).

Incremental exercise (Study II): This exercise profile consisted of four consecutive, 6-min periods of incremental exercise at ergometer workloads of 50, 100, 150, and 200 W. The 24-min period of continuous, incremental exercise was preceded and followed by 30-min rest and recovery periods for a total O_2 exposure of 84 min.

Measurement Sequences

The sequence and timing of measurements for the alternating rest and exercise profile are summarized in Fig. 1. Visual evoked responses, visual acuity, accommodation, pupillometry, and retinal electrical activity were measured at 1.0 ATA before and after the oxygen-exercise exposure at 2.0 ATA. During O_2 exposure at 2.0 ATA, inspiratory flow, deep body temperature, end-tidal P_{CO_2}, and mask O_2 concentration were monitored continually at rest and during exercise. Brain electrical activity was also monitored continuously, but intervals of total relaxation were scheduled during the rest periods to ensure artifact-free recordings. Visual fields, pulmonary function, and mental performance were evaluated at rest while breathing O_2 before and after the first exercise period, and while breathing air at 2.0 ATA after the second exercise period. Cardiovascular function, rate of CO_2 elimination, and arterial blood gases were measured during each rest and exercise period at 2.0 ATA.

Prior to the 2.0 ATA O_2 exposure, cardiorespiratory responses to the alternating rest and exercise profile were measured during air breathing at 1.0 ATA to obtain accurate measurements of O_2 uptake at the selected workload. It also provided valuable training for the subjects and confirmed that they could complete two 30-min exercise periods separated by a 30-min rest.

Measurement sequences for the incremental exercise profile were similar to those described above for intermittent exercise at 2.0 ATA (Fig. 1). Visual measurements were obtained at 1.0 ATA before and after the 2.0 ATA oxygen-exercise exposure. Measurement sequences at 2.0 ATA during the 30-min rest periods that preceded and followed the 24-min period of incremental exercise were identical to those shown for the rest periods in Fig. 1. Arterial blood gases were also measured at rest during 10-min periods of normoxia at 2.0 ATA before and after the 84-min O_2 exposure.

Central Nervous System/Visual Function

Electroencephalography: A 12-channel EEG was continuously recorded from 16 scalp electrodes onto an EEG machine (Model 8-16, Grass Instruments Co., Quincy, MA) and onto a magnetic tape recorder (TEAC

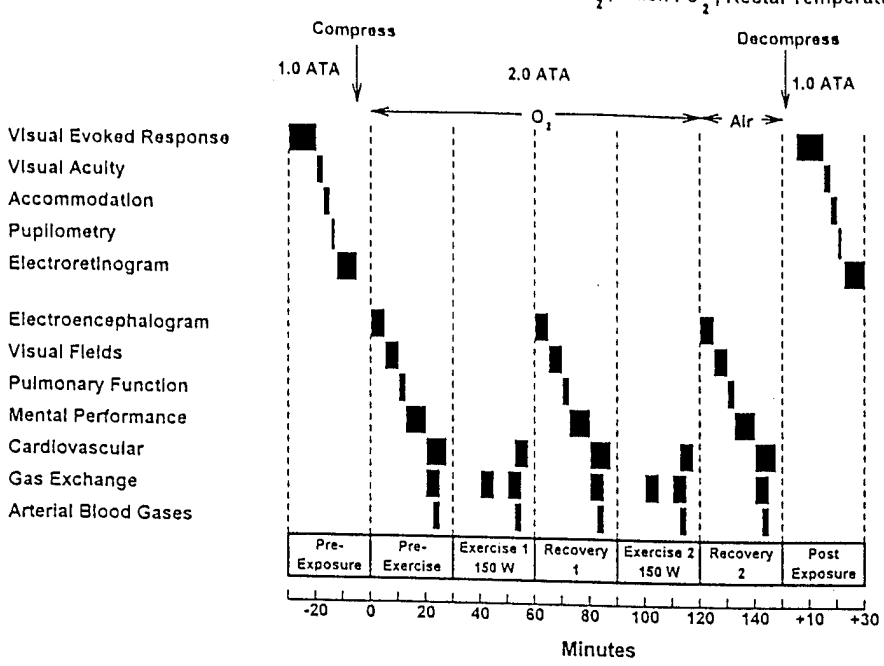

Fig. 1. Sequence and timing of measurements for alternating rest and exercise profile.

Model XR510, Montebello, CA). A modified INT 10-20 system was used for electrode placement.

Mental performance: Mental and psychomotor function were evaluated before and after each period of exercise. Specific tests included a visual digit span test of short term memory ability, a key insertion test of finger dexterity ability, an operations test of number facility and general reasoning abilities, and a visual reaction time test of response speed ability. They were automatically administered and scored over a 7-min period by computer as a component of the Institute-developed Performance Measurement System (12) (PMS Mark II, Ecosystems, Inc., Philadelphia, PA).

Electroretinography: The electroretinogram (ERG) was obtained from the dark adapted (right) eye, using an electrode (ERG-jet, UNIVERSO SA, Switzerland) that rested on the cornea. The stimulus was a 10-μs flash (0.065 foot-candles) from a Photostimulator (Model PS22, Grass Instruments Co., Quincy, MA) outside the chamber. The flashtube housing (sealed and purged with N_2) inside the chamber was mounted onto a standard Ganzfeld apparatus (Krebs Instruments, Little Ferry, NJ). The ERG signal was magnified (Model P511 Amplifier, Grass Instruments Co.) and stored in a Signal Analyzer (Model 3561A, Hewlett-Packard Co., Palo Alto, CA). Hard copy was obtained on a Graphic Printer (Model 2671-G, Hewlett-Packard Co.). The largest β-wave amplitude obtained in two or three trials was used.

Perimetry: Peripheral visual field measurements were made monocularly on the light adapted (left) eye with the right eye patched and the chamber totally darkened. Perimetric fields were plotted every 30° on a Rodenstock Projection Perimeter (G. Rodenstock Instruments GMBH, Munich, Germany) using the 1.12 mm test spot. Field luminance of the hemisphere was fixed at 0.50 log mL, while luminance of the test spot was maintained at 2.0 log mL. The stimulus was presented randomly in any of the 12 selected field locations, with each presentation being from the "not seen" to the "seen" mode. Responses to two complete sets of presentations were averaged for each visual field measurement.

Visual evoked cortical responses: The pattern reversal visual evoked cortical response (VER) was obtained with a Pattern Reversal Stimulator (Model D112, Medical System Corp., Great Neck, NY) outside the chamber projecting onto a rear projection screen inside the chamber via a viewport. The subject was seated with his eye at a distance of 1 m from the screen. The signal from the scalp EEG electrodes (F_z/O_z) was magnified by the Grass P511 Amplifier and sent to the Hewlett-Packard 3561A Signal Analyzer for signal averaging and recording by the Graphic Printer.

Visual acuity: Central visual acuity was measured using a test chart with illuminance adjusted to 0.95 log lux (approximately equivalent to average daylight). Eye position of the seated subject was maintained at a fixed distance of 35 cm from the chart surface by a restraining device which rested on the bridge of his nose and cheekbones. Visual acuity of the left eye was measured with the right eye patched.

Accommodation: Accommodative near-point was measured with a modified Adler Near-Point Rule (Krebs Instruments, Little Ferry, NJ) as the average of at least 5 readings. All trials were performed with chamber lights on full brightness (0.5 log lux illuminance at eye level).

Pupilometry: Diameter of the left pupil was estimated to the nearest 0.5 mm by matching pupil size with the range of similar test circles on a standard chart while the subject looked directly at a 100-W chamber light fixture.

Ventilation and Gas Exchange

During the entire oxygen exposure at 2.0 ATA, inspiratory flow was measured and recorded with a pneumo-

tachygraph (Fleisch #4, Metabo, Epalinges/Lausanne, Switzerland) on the inspiratory side of the gas administration system. During periods of supine rest, timed collections of expired gas were made in a meteorological balloon (No. 100 MRL, Kaysam Corp., Totowa, NJ) which was then evacuated to 1.0 ATA for measurement of volume in a wet test gasometer (Model A1-21-1, American Meter Co., Erie, PA). Mean expired CO_2 and mask O_2 concentrations and end-tidal P_{CO_2} were measured at 1.0 ATA with calibrated gas analyzers (Models CD-3A and S-3A, Ametek/Thermox Div., Pittsburgh, PA and Model LB-2, SensorMedics Corp., Anaheim, CA, respectively). A solenoid valve that was closed during expiration and opened briefly at the start of inspiration allowed intermittent sampling of end-tidal gas from the distal side of the mask expiratory valve.

Arterial Blood Gases

Arterial blood was sampled anaerobically from a radial artery into precision-bored glass syringes by standard procedures. Analyses for pH, P_{CO_2}, and P_{O_2} were performed in duplicate with an electrode block especially adapted for use at increased ambient pressure. The electrode block (from Model 168, Ciba Corning Diagnostics Corp., Medfield, MA) was maintained at 37.0°C, and measured values were corrected to body temperature. Rectal temperature was recorded continuously using a thermistor thermometer with a range of 35 to 45°C (Model 46, Yellow Springs Instrument Co., Yellow Springs, OH).

Pulmonary Function

Flow volume loops were obtained both inside and outside the chamber using dry sealed spirometers (Models 827 and 840, Ohio Medical Products, Madison, WI) with microcomputer software (UCI/IBM, Vacumed, Ventura, CA). All lung volumes and flow rates were corrected to BTPS conditions.

Cardiovascular Functions

The ECG was monitored continuously on a Clinical Monitor (Model Sirecust 400, Siemens Corp., Iselin, NJ) and recorded onto magnetic tape. Cardiac stroke volume was measured with the aid of a Minnesota Impedance Cardiograph (Model 304A, Instrumentation For Medicine Inc., Greenwich, CT) whose outputs were recorded onto a strip chart recorder (Model Dash IV, Astro-Med, Inc., West Warwick, RI). Cardiac output was calculated as the product of heart rate and stroke volume. Blood pressure was measured via an indwelling arterial catheter using a disposable blood-pressure transducer (Transpac II, Abbott Critical Care Systems, Salt Lake City, UT) coupled to the Siemens Patient Monitor. The pulse waveform was recorded onto the Astro-Med recorder. An orthostatic maneuver was performed at selected intervals by having the subject rise from the supine to the standing position in a rapid but controlled maneuver while ECG, heart rate, blood pressure, and cardiac stroke volume were recorded.

Statistical Analysis

Paired *t*-tests were performed on the measurements of visual function which were made before and after the air control exposures at 1.0 ATA, as well as before and after the oxygen-exercise exposures at 2.0 ATA (Fig. 1). They were also used for the visual field measurements obtained before and after each exercise period at 2.0 ATA.

Analysis of variance techniques were applied to all data except the measurements of visual function. One-way ANOVA with repeated measures was used where the comparisons of interest were within an individual experimental protocol. Significance levels were adjusted by the Bonferroni method for the number of comparisons. ANOVA for two factors with repeated measures was used to determine whether responses to two 30-min periods of exercise were different for air at 1.0 ATA and O_2 at 2.0 ATA. Overall main effects were tested for each variable, followed by tests of the simple main effects between the two O_2 pressures for each period of exercise, even where the overall effect was not significant. All tests were made at the 5% level.

RESULTS

Of all the CNS and cardiorespiratory functions that were monitored before, during, and after oxygen-exercise exposure at 2.0 ATA, the most relevant to CNS O_2 tolerance are the arterial P_{CO_2} elevations observed during exercise. Ventilatory and blood gas responses to both exercise profiles will therefore be presented first, followed by summaries of all the other measurements. For parameters that were not significantly altered by either of the two exercise profiles, average responses to only the alternating rest and exercise profile will be presented. Complete tables of data for all measured variables are available upon request (8).

Pulmonary Ventilation and Gas Exchange

Average measurements of pulmonary ventilation and rate of CO_2 elimination are summarized in Tables I and II, respectively, for the 10 subjects who performed the alternating rest and exercise profile and the 6 subjects who completed the incremental exercise profile.

Rate and pattern of ventilation: For the alternating rest and exercise profile, ventilation increased during each exercise period and decreased during the subsequent recovery period (Table I). Average ventilatory responses to the same workload during air breathing at 1.0 ATA were 54.56 and 54.23 $L \cdot min^{-1}$, but these values were not significantly greater than the corresponding values for O_2 breathing at 2.0 ATA (Table I). When incremental exercise was performed during O_2 breathing at 2.0 ATA, the increased levels of ventilation were achieved by progressive increments in both tidal volume and breathing rate (Table II).

Oxygen uptake and carbon dioxide elimination rates: Average rates of O_2 uptake and CO_2 elimination in 10 subjects during the first and second exercise periods while breathing air at 1.0 ATA were 1.868 and 1.873 $L \cdot min^{-1}$, respectively, for O_2, and 1.841 and 1.817 $L \cdot min^{-1}$ for CO_2. Corresponding rates of CO_2 elimination at the same ergometer workload during O_2 breathing at 2.0 ATA were smaller (Table I), but the differences were not significant statistically. Average

TABLE I. EFFECTS OF INTERMITTENT EXERCISE ON VENTILATION AND GAS EXCHANGE DURING AND AFTER OXYGEN EXPOSURE AT 2.0 ATA IN MAN.

	$\dot{V}_E$ (L · min^{-1}, BTPS)	V_T (L, BTPS)	f (br/min)	$\dot{V}_{CO_2}$ (L · min^{-1}, STPD)
Pre-Exercise	9.41 ± 2.26	0.608 ± 0.183	16.1 ± 4.1	0.229 ± 0.039
Exercise 1	52.44 ± 15.01	1.721 ± 0.292	30.4 ± 6.3	1.802 ± 0.456
Recovery 1	11.05 ± 1.58	0.625 ± 0.074	17.9 ± 3.5	0.272 ± 0.037
Exercise 2	51.96 ± 11.90	1.711 ± 0.190	30.4 ± 5.9	1.734 ± 0.323
Recovery 2*	9.72 ± 1.55	0.565 ± 0.088	17.6 ± 4.2	0.287 ± 0.040

Mean ± S.D.; N = 10.
* Breathing air at 2.0 ATA.
Statistically significant differences which reflect known responses to exercise are not indicated in the table.

TABLE II. EFFECTS OF INCREMENTAL EXERCISE ON VENTILATION AND GAS EXCHANGE DURING AND AFTER OXYGEN EXPOSURE AT 2.0 ATA IN MAN (SUBJECTS WHO COMPLETED ALL WORK LOADS).

	$\dot{V}_E$ (L/min, BTPS)	V_T (L, BTPS)	f (br/min)	$\dot{V}_{CO_2}$ (L/min, STPD)
Normoxia*	8.02 ± 1.75	0.586 ± 0.169	14.3 ± 3.4	0.204 ± 0.026
Pre-Exercise	10.30 ± 1.33	0.674 ± 0.174	15.9 ± 3.3	0.226 ± 0.048
Exercise-50	25.95 ± 3.45	1.213 ± 0.158	21.8 ± 4.3	0.713 ± 0.033
Exercise-100	36.33 ± 4.90	1.549 ± 0.137	23.6 ± 3.7	1.069 ± 0.062
Exercise-150	48.46 ± 5.96	1.736 ± 0.216	28.2 ± 4.0	1.578 ± 0.075
Exercise-200	66.09 ± 9.77	2.051 ± 0.259	32.6 ± 5.6	2.276 ± 0.155
Recovery	11.69 ± 1.90	0.604 ± 0.103	19.5 ± 2.0	0.245 ± 0.034
Normoxia*	8.12 ± 0.89	0.504 ± 0.066	16.4 ± 3.1	0.197 ± 0.029

Mean ± S.D., N = 6.
* Normoxic inspired gas at 2.0 ATA.
Statistically significant differences which reflect known responses to exercise are not indicated in the table.

rates of CO_2 elimination (N = 6) during incremental exercise while breathing O_2 at 2.0 ATA are shown in Table II.

Arterial blood gases: Average values of arterial PO_2, Pco_2, pH, and [Hco_3^-] measured before, during, and after two 30-min periods of oxygen-exercise exposure at 2.0 ATA are summarized in Table III. Average arterial Pco_2 during O_2 breathing at 2.0 ATA rose from a resting value of 38.1 to 43.3 mm Hg for the first work period, fell to 38.3 mm Hg for the first recovery period, and rose to 42.8 mm Hg for the second work period. Both increments in arterial Pco_2 during exercise were statistically significant. Individual changes in arterial Pco_2 during exercise ranged from −0.2 to 10.8 mm Hg in different subjects.

Average values of arterial Po_2, Pco_2, pH, and [Hco_3^-] measured before, during, and after the incremental exercise profile are shown in Table IV. Average arterial Pco_2 values during O_2 breathing at 2.0 ATA for the 6 subjects who performed all 4 workloads increased significantly from 34.3 mm Hg at rest to 36.8, 38.9, 41.6, and 44.0 mm Hg, respectively, at the four incremental workloads. When plotted against rate of CO_2 elimination as an index of workload, the data show a nearly linear increase in arterial Pco_2 as workload is increased during O_2 breathing at 2.0 ATA (Fig. 2).

Individual values of arterial Pco_2 for the 6 subjects who completed all 4 incremental workloads are shown in Fig. 3. Prior to the start of exercise, the consistent decrement in arterial Pco_2 during the transition from normoxia to O_2 breathing at 2.0 ATA was associated with a concurrent increment in ventilation (Table II). The reverse transition after termination of exercise was associated with an elevation in Pco_2 in 5 of the 6 subjects. During the period of incremental exercise, all 6 subjects had progressive elevations in arterial Pco_2 as workload increased. Arterial Pco_2 increments at the highest workload ranged from 4.4 to 14.2 mm Hg in individual subjects.

Brain Electrical Activity

Online inspection of the EEG records during each oxygen-exercise exposure revealed no evidence of increased excitability or other abnormalities at rest or during exercise.

Mental and Psychomotor Performance

Average scores for each of the administered tests were remarkably similar before and after each 30-min period of exercise during O_2 breathing at 2.0 ATA (Table V). Scores obtained before and after 24 min of incremental exercise while breathing O_2 at 2.0 ATA were also similar (not shown).

Visual Function

Measurements obtained before and after two 30-min periods of exercise during O_2 exposure at 2.0 ATA are summarized in Table VI. Most of the average values of visual function parameters measured before and after oxygen-exercise exposure were nearly identical. Any

TABLE III. EFFECTS OF INTERMITTENT EXERCISE ON ARTERIAL Po_2, Pco_2, pH, and $[Hco_3^-]$ DURING AND AFTER OXYGEN EXPOSURE AT 2.0 ATA IN MAN.

	Po_2 (mm Hg)	Pco_2 (mm Hg)		pH		$[Hco_3^-]$ (meq/L)
Pre-Exercise	1306 ± 60*	38.1 ± 4.5	‡	7.422 ± 0.033	‡	24.5 ± 2.7
Exercise 1	1305 ± 39*	43.3 ± 4.3		7.347 ± 0.067		23.4 ± 2.7
Recovery 1	1324 ± 46*	38.3 ± 5.8	‡	7.410 ± 0.044	‡	23.8 ± 2.4
Exercise 2	1324 ± 54*	42.8 ± 3.8		7.372 ± 0.043		24.4 ± 1.1
Recovery 2*	280 ± 31*	43.2 ± 4.4		7.382 ± 0.034		25.2 ± 1.8

Mean ± S.D., N = 10, *N = 9.
† Breathing air at 2.0 ATA.
‡ Statistically significant ($p \leq 0.05$) difference between mean values indicated by brackets. Determined by *t*-test adjusted for multiple comparisons following analysis of variance.

observed differences were well within the range of random variability and were not statistically significant. Similar agreement was found for the measurements obtained before and after the incremental exercise profile (not shown).

Pulmonary Function

Average values of forced vital capacity (FVC), 1-s forced expired volume (FEV_1), peak expiratory flow rate (PEFR), and maximal mid-expiratory flow rate (FEF_{25-75}) obtained before and after each period of exercise are listed in Table VII. Average FVC and FEV_1 either remained essentially unchanged or were slightly increased after each period of exercise. The FVC increments were statistically significant after both 30-min periods of exercise, while the increments in FEV_1 were significant only after the second exercise period. Average PEFR and FEF_{25-75} were also unchanged or slightly increased. None of the changes in PEFR were statistically significant, and FEF_{25-75} was significantly increased only after the second 30-min exercise period.

There were no significant changes in lung volumes or flow rates after incremental exercise during O_2 breathing at 2.0 ATA (not shown). The data show that pulmonary mechanical function was either not changed or was slightly improved by exercise even when combined with O_2 exposure at 2.0 ATA. Similar effects of exercise on pulmonary mechanical function have been attributed to reduction in airway resistance to flow caused by exercise-induced alterations in the autonomic control of bronchomotor tone (14).

Cardiovascular Function

Average values of heart rate, stroke volume, cardiac output, arterial blood pressure, and deep body temperature measured before, during, and after each period of exercise while breathing O_2 at 2.0 ATA are summarized in Table VIII. All changes in deep body temperature and both systolic and diastolic blood pressure were appropriate for the corresponding level of exercise and did not appear to be significantly influenced by ambient pressure or inspired Po_2.

Average heart rates were consistently lower during O_2 breathing at 2.0 ATA than for air breathing at 1.0 ATA. Control values (mean ± S.D.) for air breathing at 1.0 ATA were 58.9 ± 4.4 beats · min^{-1} at rest, 144.6 ± 18.1 during the first exercise period, 76.1 ± 12.6 during the first recovery period, 151.1 ± 16.7 during the second exercise period, and 78.5 ± 12.5 during the final recovery period. All differences between 1.0 and 2.0 ATA values were statistically significant except for the pre-exercise resting control value. Average values of stroke volume were consistently higher at 2.0 ATA, but the difference was statistically significant only for the second recovery period (135.2 ± 41.8 ml at 2.0 ATA vs. 107.7 ± 35.4 ml at 1.0 ATA). Average cardiac output

TABLE IV. EFFECTS OF INCREMENTAL EXERCISE ON ARTERIAL Po_2, Pco_2, pH, and $[Hco_3^-]$ DURING AND AFTER OXYGEN EXPOSURE AT 2.0 ATA IN MAN (SUBJECTS WHO COMPLETED ALL WORK LOADS).

	Po_2 (mm Hg)	Pco_2 (mm Hg)		pH		$[Hco_3^-]$ (meq/L)
Normoxia*	121 ± 16	40.5 ± 2.9		7.384 ± 0.012		23.9 ± 2.2
Pre-Exercise	1340 ± 52	34.3 ± 1.7		7.434 ± 0.025		22.9 ± 2.1
Exercise-50	1322 ± 27	36.8 ± 3.9		7.418 ± 0.028		23.5 ± 2.5
Exercise-100	1343 ± 32	38.9 ± 4.6	†	7.400 ± 0.027	†	23.9 ± 2.8
Exercise-150	1351 ± 41	41.6 ± 4.2		7.380 ± 0.022		24.2 ± 2.5
Exercise-200	1327 ± 48	44.0 ± 5.5		7.346 ± 0.029		23.6 ± 2.6
Recovery	1335 ± 58	35.0 ± 3.3		7.436 ± 0.035		23.4 ± 2.2
Normoxia*	118 ± 25	39.5 ± 2.8		7.400 ± 0.022		24.2 ± 2.5

Mean ± S.D., N = 6.
* Normoxic inspired gas at 2.0 ATA.
† Statistically significant ($p \leq 0.05$) trend across increasing work loads for values enclosed within brackets.

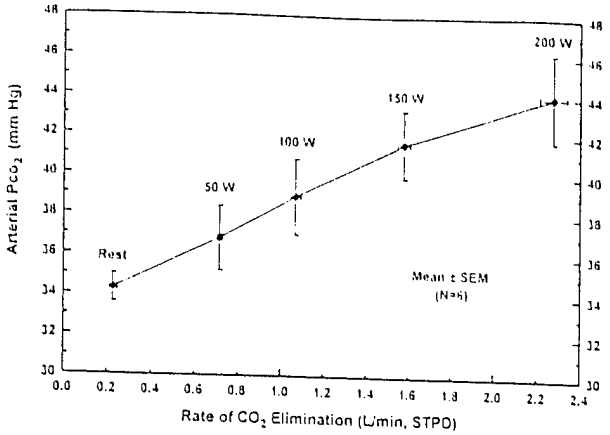

Fig. 2. Relationship of arterial Pco_2 to rate of CO_2 elimination during incremental exercise while breathing O_2 at 2.0 ATA. Average values are shown for the 6 subjects who were able to complete all 4 workloads. Bars represent 1 standard error of the mean.

responses to 30-min periods of exercise were slightly lower at 2.0 ATA, but the differences were not significant.

Complete measurements of cardiac responses to incremental exercise during O_2 exposure at 2.0 ATA were obtained in only 5 of the 6 subjects who performed all 4 workloads. Average heart rate increased progressively from a value of 50.0 beats • min^{-1} at rest to 78.6, 89.6, 110.4, and 133.2 beats • min^{-1} at workloads of 50, 100, 150, and 200 W, respectively. Average values of stroke volume were 138.3 ml at rest and 130.8, 133.5, 128.2, and 105.8 ml during exercise. Corresponding values of cardiac output were 6.90 L • min^{-1} at rest and 10.34, 12.14, 14.24, and 14.20 L • min^{-1} at the 4 workloads. All three trends were statistically significant. The average maximum workload for these subjects during air breathing at 1.0 ATA was 240 W for 3 min. The apparent plateauing of cardiac output over the two highest workloads concurrently with a nearly linear increase in heart rate and terminal fall in stroke volume are all consistent with physiological responses to near maximal exercise.

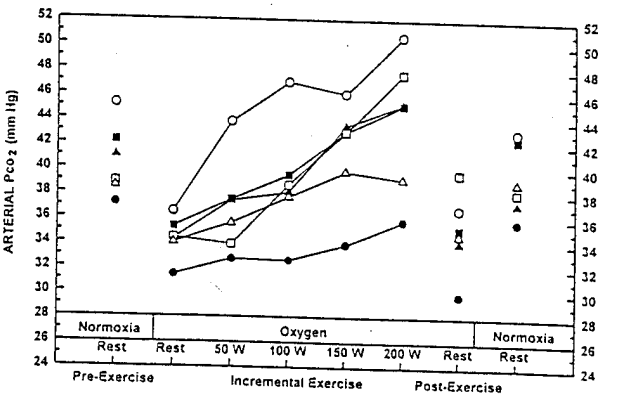

Fig. 3. Individual arterial Pco_2 responses to incremental exercise while breathing O_2 at 2.0 ATA. Data are shown for the 6 subjects who completed all 4 workloads. Values for each subject are represented by a different symbol. Normoxic values were obtained at rest pre-exercise and during the post-exercise recovery period while breathing 10.5% O_2 in N_2 at 2.0 ATA. All other values were obtained while breathing 100% O_2.

DISCUSSION

Oxygen exposures at 2.0 ATA for a total duration 120 min with two 30-min periods of moderately hea exercise have been completed in 10 subjects with detectable impairment of visual function or decremer in mental and psychomotor performance. There we no indications of incipient convulsions or other mar festations of CNS O_2 toxicity. In addition, repeat measurements of ventilatory and cardiovascular r sponses, both at rest and during exercise, and of pu monary mechanical function during the resting recove after each of the two 30-min exercise periods reveal none of the toxic effects that were observed during th previously completed, prolonged resting exposures O_2 pressures of 3.0, 2.5, 2.0, or 1.5 ATA for avera durations of 3.4, 5.7, 9.0, and 17.7 h, respective (6,7,13,18,26).

These measurements together establish for the fir time that multiple CNS and cardiopulmonary functio remain unimpaired under conditions of exercise and e exposure in a dry chamber that appear to equal or e ceed the limits of CNS O_2 tolerance in working dive (4). This is in accord with the previous finding of norm hearing and cognitive function within 4–30 min prior a convulsion experienced by a resting subject after 3.0 of O_2 breathing at 3.0 ATA (18).

Comparison of Present Results with Previous Studies of Exercise Effects on CNS Oxygen Tolerance

Previous studies have demonstrated adverse effec of exercise on CNS O_2 tolerance in man (3,4,11,24,29 Of these studies, the carefully documented and rel tively recent observations of Butler and Thalmann (3,4 are most appropriate for comparison with the preser study. In one series of experiments, these investigator carried out 40 man-dives at 35 fsw (2.06 ATA) with 3 min of continuous exercise at a workload of 1.6 L • min^{-1}. Four divers developed leg twitching at 25 t 29.5 min of exposure to give a 10% incidence of definit CNS symptoms.

Our observation that no detectable effects of CN toxicity occurred in 10 subjects who performed two 30 min periods of exercise while breathing O_2 at 2.0 ATA for 120 min does not differ significantly from the result cited above. However, several factors should be con sidered in comparing results of the two studies. Defin tion of CNS O_2 convulsion latency in man must tak into account well-documented variation in toleranc among different individuals exposed to the same condi tions (5,11). In addition, there are indications that an O pressure of 2.0 ATA lies near an "asymptote" o threshold of O_2 convulsion latency (5) where small dif ferences in inspired Po_2 will have relatively large influ ences on onset times of overt toxic effects. Although th physiological basis has not been explained, immersio has been associated with decreased CNS O_2 toleranc at rest and during exercise (11,29). The divers studie by Butler and Thalmann worked underwater using closed-circuit underwater breathing apparatus, whil our subjects performed exercise in a dry chamber usin a low resistance, open-circuit breathing system. Studie designed to evaluate possible influences of immersion

TABLE V. EFFECTS OF INTERMITTENT EXERCISE ON MENTAL AND PSYCHOMOTOR FUNCTION DURING AND AFTER OXYGEN EXPOSURE AT 2.0 ATA IN MAN.

	Visual Digit Span (correct responses)	Key Insertion (correct responses)	Operations (correct–incorrect/3)	Visual Reaction Time (s)
Pre-Exercise	35.7 ± 5.6	55.3 ± 10.7*	45.3 ± 5.4	0.275 ± 0.036
Recovery 1	37.0 ± 5.5	53.6 ± 8.9*	45.8 ± 5.1	0.280 ± 0.020
Recovery 2†	34.2 ± 4.0	57.8 ± 6.5*	45.2 ± 5.2	0.279 ± 0.037

Mean ± S.D., N = 10.
* N = 9.
† Breathing air at 2.0 ATA.
Data collected at rest before and after each exercise period.

TABLE VI. EFFECTS OF INTERMITTENT EXERCISE ON VISUAL FUNCTION DURING AND AFTER OXYGEN EXPOSURE AT 2.0 ATA IN MAN.

	Visual Acuity	Accommodation (Near-point, cm)	Pupil Diameter (mm)	Electroretinogram (Amplitude, mV)	Visual Evoked Response (Latency, ms)	Visual Fields (Relative Area)
Pre-Exposure	20/20	11.6 ± 1.9	3.8 ± 0.5	327 ± 54	114 ± 6	
Pre-Exercise						1.00
Recovery 1						0.99 ± 0.08
Recovery 2*						0.99 ± 0.15
Post-Exposure	20/20	11.6 ± 1.9	3.8 ± 0.4	344 ± 72	110 ± 6	

Mean ± S.D., N = 10.
* Breathing air at 2.0 ATA.
Data collected at 1.0 ATA before and after oxygen exposure at 2.0 ATA, except for visual fields which were measured at 2.0 ATA before and after each exercise period.

TABLE VII. EFFECTS OF INTERMITTENT EXERCISE ON PULMONARY FUNCTION DURING AND AFTER OXYGEN EXPOSURE AT 2.0 ATA IN MAN.

	FVC (L)	LEV_1 (L)	PERF ($L \cdot s^{-1}$)	FEF_{25-75} ($L \cdot s^{-1}$)
Pre-Exercise	5.03 ± 0.80	3.67 ± 0.51	6.62 ± 0.82	3.08 ± 0.72
Recovery 1	5.15 ± 0.89†	3.73 ± 0.52	6.66 ± 1.43	3.13 ± 0.85
Recovery 2*	5.14 ± 0.89†	3.86 ± 0.52†	7.01 ± 1.41	3.41 ± 0.83†

Mean ± S.D., N = 10.
* Breathing air at 2.0 ATA.
† Difference from Pre-Exercise statistically significant, $p \leq 0.05$.
Data collected at rest before and after each exercise period.

TABLE VIII. EFFECTS OF INTERMITTENT EXERCISE ON CARDIOVASCULAR FUNCTION AND CORE TEMPERATURE DURING AND AFTER OXYGEN EXPOSURE AT 2.0 ATA IN MAN.

	Heart Rate (bpm)	Stroke Volume (ml)	Cardiac Output ($L \cdot min^{-1}$)	Systolic B.P. (mm Hg)	Diastolic B.P. (mm Hg)	Core Temp (°C)
Pre-Exercise	54.8 ± 4.5	153.9 ± 36.4	8.38 ± 1.91	139.5 ± 11.2	73.6 ± 10.3	36.9 ± 0.3
Exercise 1	129.2 ± 14.5	132.1 ± 28.7	17.00 ± 4.07	169.8 ± 29.0	72.7 ± 10.8	37.3 ± 0.3
Recovery 1	61.2 ± 10.0	132.0 ± 38.1	7.96 ± 2.26	127.1 ± 8.6	63.8 ± 5.4	37.4 ± 0.3
Exercise 2	134.8 ± 17.1	136.2 ± 27.8	18.40 ± 4.80	160.3 ± 27.7	73.1 ± 10.8	37.6 ± 0.4
Recovery 2*	61.2 ± 11.9	135.2 ± 41.8	8.09 ± 2.23	125.2 ± 8.4	66.3 ± 9.5	37.4 ± 0.5

Mean ± S.D., N = 10.
* Breathing air at 2.0 ATA.
Statistically significant differences which reflect known responses to exercise are not indicated in the table.

hyperoxia itself, and increased work of breathing on ventilatory and cerebral circulatory responses to exercise are feasible and required.

Ventilatory Responses to Hyperoxia at Rest and During Exercise

When O_2 is breathed at 2.0 ATA, each 100 ml of arterial blood contains about 4.4 ml of O_2 as compared to only 0.3 ml during air breathing at 1.0 ATA (17). As a result of the contribution of this increased volume of physically dissolved O_2 to tissue metabolic demands, less O_2 is removed from hemoglobin which in turn becomes less able to bind CO_2. The decrement in hemoglobin-bound CO_2 is associated with a corresponding increment in physically dissolved CO_2 and concurrent increments in tissue P_{CO_2} and $[H^+]$. The subsequent

stimulation of central respiratory chemoreceptors is partially opposed by a concurrent, oxygen-induced depression of peripheral chemoreceptors (17,21,22). Once a steady-state has been achieved, the net effect at rest is a mild level of hyperventilation hypocapnia that persists even when the O_2 exposure is continued for many hours (13).

Although the net ventilatory stimulation and arterial hypocapnia induced by hyperoxia are readily evident at rest, ventilatory responses to exercise during O_2 breathing at 2.0 ATA are such that arterial Pco_2 rises progressively with increasing workload (Figs. 2,3). This pattern differs from the corresponding relationship of arterial Pco_2 to incremental exercise during air breathing at 1.0 ATA, where endurance-trained athletes typically have a slight increase in alveolar or arterial Pco_2 at low workloads followed by a progressive fall at higher workloads (9,10).

Direct measurements of ventilatory responses to the same workload during air breathing at 1.0 ATA and O_2 breathing at 2.0 ATA in the present subjects showed that average values during O_2 breathing were decreased by about 2 $L \cdot min^{-1}$, and this small difference was not statistically significant. However, examination of the reciprocal relationship between arterial Pco_2 and alveolar ventilation indicates that, at the selected workload, an arterial Pco_2 elevation of 1 mm Hg would require a ventilatory decrement of only about 1 $L \cdot min^{-1}$. Thus, the measured average ventilation values, obtained on two different days, are consistent with the observed change in arterial Pco_2.

Previous investigators have also found end-tidal Pco_2 elevations during exercise while breathing O_2 at 1.0 ATA (1,2,15) and exercise-induced elevations in arterial Pco_2 during O_2 breathing at 2.0 ATA (28). The multiple influences that may contribute to reduced ventilatory responses to exercise during O_2 breathing at 2.0 ATA include hyperoxic suppression of the ventilatory response to hypercapnia (21,25), the greater work of breathing caused by increased gas density (24), and the reduced level of metabolic acidosis associated with O_2 breathing at 2.0 ATA (23).

Hypercapnia Influences on Oxygen Tolerance

Our results show that the physiological responses to exercise while breathing O_2 at 2.0 ATA include a consistent elevation in arterial Pco_2 (Table III) that is progressive with increasing workload (Figs. 2,3). This physiological response is highly relevant to the adverse effects of exercise on CNS O_2 tolerance, because CO_2 hastens the onset of O_2 convulsions (19), apparently by increasing cerebral blood (O_2) flow (16,19,27) and brain venous Po_2 (19).

In a group of divers who performed tethered swimming (O_2 uptake about 1.4 $L \cdot min^{-1}$) while breathing 45% O_2/55% N_2 at 4.0 ATA, Lanphier (24) found that convulsions and other manifestations of CNS O_2 toxicity occurred more rapidly than expected on the basis of previous determinations of CNS O_2 tolerance during underwater exercise while breathing 100% O_2 at an equivalent pressure of 1.8 ATA. Subsequent measurements of end-tidal Pco_2 during exercise in the same divers revealed average values of about 47 mm Hg while breathing air at 1.0 ATA, 49 mm Hg on O_2 at 1.8 ATA, and 55 mm Hg on 45% O_2/55% N_2 at 4.0 ATA. Lanphier concluded that arterial Pco_2 elevation provided a plausible explanation for the more rapid onset of CNS O_2 toxicity in divers breathing the nitrox mixture at 4.0 ATA.

Results of the present study also indicate that exercise while breathing 100% O_2 at 2.0 ATA could decrease CNS convulsion latency by increasing arterial Pco_2 with related increments in brain blood flow and O_2 dose. Although direct measurements of cerebral venous Po_2 under such conditions are not available, the order of magnitude of Po_2 elevation can be approximated from measurements of arterial Pco_2 and internal jugular venous Po_2 in four men who breathed 100% O_2 and 2% CO_2 in O_2 at 3.5 ATA (19). In the transition from O_2 to O_2-CO_2, average arterial Pco_2 rose from 37 to 58 mm Hg, with corresponding jugular venous Po_2 values of 76 and 1000 mm Hg, respectively. Although a comparable degree of rise in brain venous Po_2 would not be expected during O_2 breathing at 2.0 ATA with an arterial Pco_2 elevation of 14 mm Hg at most (Fig. 3), this degree of hypercapnia should increase brain Po_2 significantly. Concurrent measurements of arterial Pco_2 and cerebral blood flow at rest and during exercise while breathing O_2 at 2.0 ATA are needed to explore this possibility.

It is known that some divers are individually predisposed to the development of hypercapnia during exercise (24). It is also known that external factors such as excessive breathing resistance can have similar effects even in individuals who have normal CO_2 tolerance (24). Additional studies of arterial Pco_2 and cerebral circulatory responses to combined exercise and hyperoxia are required to evaluate the relevance of such factors to the adverse effects of exercise on CNS O_2 tolerance.

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RELATIONSHIP OF ^{133}XE CEREBRAL BLOOD FLOW TO MIDDLE CEREBRAL ARTERIAL FLOW VELOCITY IN MAN AT REST

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ABSTRACT

Cerebral blood flow (CBF) was measured by ^{133}Xe clearance simultaneously with velocity of blood flow through the left middle cerebral artery (MCA) over a wide range of arterial Pco_2 in 8 normal men. Average arterial Pco_2, which was varied by giving 4% and 6% CO_2 in O_2 and by controlled hyperventilation on O_2, ranged from 25.3 to 49.9 mm Hg. Corresponding average values of global CBF_{15} were 27.2 and 65.0 ml/100 g/min, respectively, while MCA blood flow velocity ranged from 42.8 to 94.2 cm/sec. The relationship of CBF to MCA blood flow velocity over the imposed range of arterial Pco_2 was described analytically by a parabola with the equation:

$$\mathbf{CBF = 22.8 - 0.17 \times Velocity + 0.006 \times Velocity^2}$$

The observed data indicate that MCA blood flow velocity is a useful index of CBF response to change in arterial Pco_2 during O_2 breathing at rest. With respect to baseline values measured while breathing 100% O_2 spontaneously, percent changes in velocity were significantly smaller than corresponding percent changes in CBF at increased levels of arterial Pco_2, and were larger than CBF changes at the lower arterial Pco_2. These observed relative changes are consistent with MCA vasodilation at the site of measurement during exposure to progressive hypercapnia and also during extreme hyperventilation hypocapnia.

Index Terms: brain blood flow; brain circulation control; transcranial doppler ultrasonography; middle cerebral artery vasodilation; carbon dioxide; oxygen.

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INTRODUCTION

Transcranial doppler (TCD) ultrasonography, developed as a noninvasive technique for measuring blood flow velocity in major cerebral vessels (Aaslid et al., 1982), provides a quantitative index of cerebral blood flow (CBF) that can be measured continuously under conditions in which more direct methods (eg. that require bulky instrumentation and/or administration of radioactive isotopes) are not useful. Changes in blood flow velocity through basal cerebral arteries are stated to be closely proportional to concurrent changes in CBF (Aaslid, 1987; Aaslid et al., 1989; Lindegaard et al., 1987). This is based on the assumption that the diameters of basal cerebral vessels do not change in response to physiological stimuli which affect the brain microcirculation. In support of this assumption, angiographic measurements of human cerebral vessels (Huber and Handa, 1967) showed that vessels greater than 2.5 mm in diameter did not dilate significantly during hypercapnia, while another study (Krapf et al., 1987) showed that vasopressin administration failed to constrict either the internal carotid or middle cerebral arteries. However, other studies indicate that basal cerebral vessels do contribute to alterations in cerebral hemodynamics (Kontos et al., 1978; Wei et al., 1980). Referring to these apparently contradictory findings, Werner (1991) concluded that any representation of changes in CBF by TCD measurements of blood velocity must be supported by direct correlation of TCD data with classical measurements of CBF for each physiological condition.

If appropriately validated, TCD ultrasonography would be useful for quantitative investigation of the inter-relationships among arterial Pco_2, CBF, brain oxygen dose, and risk of oxygen convulsions in divers exposed to extreme respiratory environments and in patients who breathe oxygen therapeutically at increased ambient pressures in hyperbaric chambers (Kindwall, 1994). In military, commercial, and scientific diving operations, hyperoxia is used to enhance the safety and efficiency of decompression procedures (Lambertsen, 1967). When arterial hypercapnia occurs during exposure to hyperoxia, the risk of oxygen convulsions is increased by associated increments in brain blood flow and oxygen pressure (Lambertsen et al., 1955). In medical applications of hyperbaric oxygenation, hypoventilation imposed by pharmacologic interventions with narcotic drugs or other respiratory depressants also causes concurrent increments in arterial Pco_2, brain oxygen dose, and risk of convulsions. Quantitative definition of the interactions among these parameters would be greatly aided by the availability of a reliable CBF index that can be measured noninvasively under both steady-state and dynamic conditions.

To evaluate the use of middle cerebral artery (MCA) blood flow velocity as an index of CBF while breathing O_2 at increased ambient pressures, we concurrently measured blood flow velocity by TCD ultrasonography and CBF by ^{133}Xe clearance in normal young men at rest breathing O_2 at 1.0 atmosphere absolute (ATA), with spontaneous and altered arterial Pco_2 levels. Clearance of ^{133}Xe with administration of the tracer by inhalation was selected as the CBF method because it is widely used

(Skolnick, 1991; Young et al., 1995), noninvasive (Skolnick, 1991), and highly reproducible in normal young adults (Warach et al., 1988). Prominent changes in both CBF and blood flow velocity were assured by voluntary hyperventilation and by CO_2 administration to provide the desired wide range of arterial Pco_2. Oxygen was used as the background gas to provide the highest possible arterial Po_2 values at normal atmospheric pressure. An air breathing CBF control was not included, because previous studies appeared to indicate that CBF reductions associated with O_2 breathing could be explained by concurrent decrements in arterial Pco_2 (Kety and Schmidt, 1948; Lambertsen et al., 1953; Lambertsen, 1965; Busija et al., 1980).

METHODS

All experiments were performed within the Cerebral Blood Flow Laboratory of the Cerebrovascular Research Center at the University of Pennsylvania Medical Center. Subjects were normal men ranging in age from 21 to 40 years (mean 25.8). All subjects gave informed consent to a research protocol approved by the Human Studies Committee of the University of Pennsylvania.

The experiment protocol is summarized in Fig. 1. Arterial Pco_2 was varied by administration of 4% and 6% CO_2 in O_2 and by voluntary controlled hyperventilation while breathing 100% O_2. Prior to breathing O_2 for the first time, arterial blood was sampled and MCA blood flow velocity was measured over a 2-min period while breathing room air. The order of gas administration then proceeded as indicated in Fig. 1. Each gas mixture was breathed for 30 min. After the first 10 min, the arterial circulation was loaded with inhaled radioactive xenon (^{133}Xe) over a 1-min rebreathing period. Arterial blood sampling, CBF determination, and TCD measurement periods are as indicated. As part of the pre-experiment preparations, each subject breathed 6% CO_2 in O_2 for 30 min to become familiar with the subjective stresses induced by hypercapnia.

CBF Measurement by ^{133}Xe Clearance

The noninvasive ^{133}Xe clearance method for measuring regional CBF (rCBF) was performed in a standard manner (Skolnick, 1991). Briefly, a trace amount of ^{133}Xe, a highly diffusible gamma-emitting inert gas, was inhaled during a 1-min

period of rebreathing and passed by alveolar-capillary diffusion into the systemic circulation. On reaching the brain via the arterial circulation, ^{133}Xe diffused into the brain parenchyma in accord with its concentration gradient and partition coefficients. Clearance of the tracer was monitored for 15 min with collimated scintillation detectors (NaI crystals). The Novo Cerebrograph system (Model 32B, Helmet upgrade) used for the CBF measurement contained 32 detectors placed over 16 homotopic regions of the two hemispheres.

Both CBF_{15} and F_1 estimates of CBF were calculated from the measured rate of ^{133}Xe clearance (Obrist and Wilkinson, 1990). CBF_{15}, representing the averaged CBF of both gray and white matter, was calculated as the height-over-area for the entire 15 min of clearance. The F_1 tissue compartment that has fast clearance characteristics and primarily represents CBF in gray matter was calculated by using the biexponential least squares method. The relative weight of the F_1 compartment (w_1) was also calculated because it was considered that the imposed range of arterial Pco_2 was wide enough to cause "slippage" between compartments in a two-compartment analysis of the clearance curves.

TCD Measurement of MCA Blood Flow Velocity

MCA blood flow velocity was measured as a moving average of the mean velocity for each cardiac cycle with an Eden Medical Electronics TC 2000S Multifrequency Transcranial Doppler System using the technique of Aaslid et al (1982). A standard transtemporal window and a 2 megahertz probe stabilized with a

probe head holder were used. Acquired data were continuously stored, and average values over specific time periods (Fig. 1) were identified and extracted.

Arterial Blood Sampling and Analysis

Arterial blood was sampled anaerobically via an indwelling radial artery catheter into a precision-bored 10 ml glass syringe with heparin solution lining the walls and filling the deadspace. The syringe was sealed and immersed immediately in a mixture of water and ice. Blood samples were analysed within 30 min for pH, Pco_2, and Po_2 on an Instrumentation Laboratory System 1304 pH/Blood Gas Analyzer. All analyses were performed at least twice, with additional analyses if duplicate measurements did not agree within 0.005 units for pH or 1.0% of the absolute value for Pco_2 or Po_2. Measured blood gas and pH values were corrected for the difference between body temperature and the measurement temperature of 37.0^{o} C by using a computer program based on previously established correction factors (Severinghaus, 1966). Rectal temperature was measured with a Yellow Springs Model 43TF thermistor thermometer.

Cardiovascular Function

The electrocardiogram was continuously monitored on a Spacelabs Alpha 14 Patient Monitor. The same system was used to monitor blood pressure with an Abbott Critical Care Systems disposable blood pressure transducer connected to the indwelling arterial catheter. Heart rate and blood pressure were recorded during or immediately after each period of arterial blood sampling.

Statistical Analysis

Regression lines and 95% confidence limits were calculated by standard methods. Effects on the cardiovascular data were tested using analysis of variance (ANOVA) with repeated measures followed by t-tests comparing each condition with the 100% O_2 data when the overall F was significant. The critical value of t was adjusted to account for the fact that four comparisons were made. The level of significance was considered to be $p \leq 0.05$.

RESULTS

Table 1 contains, for all measurement conditions, average values of arterial Pco_2, pH, and Po_2, MCA flow velocity, CBF_{15} and F_1 for all 32 probes (global), heart rate, and blood pressure. Average arterial Pco_2 ranged from a low value of 25.3 mm Hg during hyperventilation to a high value of 49.9 mm Hg while breathing 6% CO_2 in O_2. Corresponding values of MCA blood flow velocity were 42.8 and 94.2 cm/sec, respectively. Average CBF_{15} and F_1 had low values of 27.2 and 35.0 ml/100 g/min, respectively, and corresponding high values of 65.0 and 91.8 ml/100 g/min. Average w_1 values were 45.5, 47.2, 46.6, and 50.0, respectively, at arterial Pco_2 levels of 25.3, 38.5, 43.6, and 49.9 mm Hg. All four w_1 values are quantitatively similar, but w_1 for the highest Pco_2 level is significantly higher than the other 3 values (ANOVA: $F=4.98$, $df=3,21$, $p=0.009$). Although the observed small increment in w_1 may not be physiologically significant, it adds further justification to the reason given below for the use of a height-over-area rather than a compartmental analysis of our CBF data.

Fig. 2 shows average values for MCA blood flow velocity and CBF_{15} plotted against arterial Pco_2. The two cerebral circulatory indices are expressed in different units of measurement, but they have similar absolute values and can be compared on the same graph. The slope of the CBF curve is nearly parallel to corresponding segments of the velocity curve in the hypercapnic region of the arterial Pco_2 range and flatter during hyperventilation hypocapnia.

In our analysis of MCA blood flow velocity as a CBF index to be used in subsequent investigations of the inter-relationships among arterial Pco_2, CBF, and brain oxygenation, we have focused on CBF_{15} rather than F_1 as the more appropriate measure of overall brain blood flow. Individual CBF_{15} values are plotted against corresponding values for MCA blood flow velocity in Fig. 3. All eight subjects had a linear or nearly linear flow-velocity relationship at arterial Pco_2 levels that were above normal, with a variable reduction in slope in the hypocapnic region of the curve corresponding to the points for breathing 100% O_2 at rest and during hyperventilation. Therefore, both linear and parabolic expressions were used to describe the observed data analytically. The linear description of the overall flow-velocity relationship from hypercapnia through hypocapnia has the following equation:

$$\mathbf{CBF = 0.75 \times Velocity - 7.60}$$

The standard error of estimate (SE_{est}) is 6.3 ml/100 g/min, and the squared correlation coefficient (R^2) is 0.87.

The simplest nonlinear description of the observed overall flow-velocity relationship is a parabola with the following equation:

$$\mathbf{CBF = 22.8 - 0.17 \times Velocity + 0.006 \times Velocity^2}$$

For comparison with the linear expression, SE_{est} is 5.4 ml/100 g/min and R^2 is 0.91. The parabolic description of the data provides a slightly better fit than the linear expression. Based on the empirical observation that the lower portion of the flow-velocity relationship is definitely nonlinear in most of the subjects (Fig. 3), the

parabolic expression was selected for further analysis. The same individual data points that are plotted in Fig. 3 are shown in Fig. 4 with the parabola whose equation is given above. The inner pair of curves enclosing the parabola represents the 95% confidence limits for calculating an average CBF_{15} from an average value of MCA blood flow velocity for a group of subjects. The outer pair of curves represents 95% confidence limits for calculating an individual CBF_{15} value from a determination of MCA blood flow velocity in one subject.

Hemodynamic responses to the selected exposure conditions are summarized in Table 1. Average heart rate decreased slightly from 60.9 to 57.3 beats/min during the transition from air to O_2 breathing, rose progressively to 70.0 beats/min while breathing 6% CO_2 in O_2, and fell to 65.1 beats/min during hyperventilation on O_2 ($F=5.16$, $df=4,28$, $p=0.003$). The pattern of change in average systolic blood pressure was similar to that of heart rate ($F=7.46$, $df=4,28$, $p=0.0003$). Diastolic blood pressure also showed a similar trend, but these changes were not statistically significant ($F=1.06$, $df=4,28$, $p=0.39$).

All subjects were able to tolerate exposure to the four experiment conditions with no significant adverse effects. A few experienced mild headaches either during or immediately after breathing 6% CO_2 in O_2 for 30 minutes.

DISCUSSION

The present study examined the relationship of CBF to MCA blood flow velocity in normal young men breathing oxygen over an arterial Pco_2 range of 25 to 50 mm Hg. Previously published comparisons of these blood flow parameters were limited to smaller ranges of arterial Pco_2 with only one or two different levels (Bishop et al., 1986; Hartmann et al., 1991; Sorteberg et al.,1989) and have yielded discordant results. In a study whose measurement conditions included only normocapnia and hyperventilation hypocapnia, Hartmann et al. (1991) concluded that MCA blood flow velocity correlated poorly with CBF. In contrast, Bishop et al. (1986) found a statistically significant correlation between concurrent responses of both flow parameters to inhalation of 5% CO_2 in air, and Sorteberg et al.(1989) found a similar positive correlation in normal subjects between sequential measurements of MCA blood flow velocity and rCBF when the data were normalized to the same end-tidal Pco_2. Sugimori et al (1995) also observed that rCBF correlated significantly with MCA flow velocity in hypertensive and diabetic patients who had varying degrees of cerebrovascular disease.

Unique features of the present study are that it includes concurrent measurements of CBF and MCA blood flow velocity in four different conditions, over a wide range of both increased and decreased levels of arterial Pco_2, and in the same group of subjects. It is also the only such comparison at hyperoxic levels of arterial Po_2. Previous investigators (Kety and Schmidt, 1948; Wasserman and Patterson,

1961) have measured CBF in normal men over wide ranges of arterial Pco_2 in an air background and found curves similar to that in Fig. 2 with a progressively increasing slope in the transition from hypo- to hypercapnic levels of arterial Pco_2. Ramsay et al (1993) also observed similar responses over a wide arterial Pco_2 range for rCBF in both gray and white matter with consistently steeper slopes in the gray matter.

Estimation of CBF from MCA Blood Flow Velocity

The parabolic flow-velocity relationship shown in Fig. 4 can be used to estimate CBF from values of mean MCA blood flow velocity obtained under dynamic or steady-state conditions. The confidence limits about this estimate vary slightly with the absolute value of the mean velocity measurement, and more prominently with respect to whether the velocity measurement represents an average value for a group of subjects or an individual value for one subject. For example, at an average velocity measurement of 42.8 cm/sec, obtained during hyperventilation while breathing O_2, the calculated CBF value is 26.9 ml/100 g/min with 95% confidence limits of $\pm$3.4 ml/100 g/min. An identical velocity measurement for one subject would predict the same CBF value, but the 95% confidence limits would widen to $\pm$11.4 ml/100 g/min. At an MCA blood flow velocity of 94.2 cm/sec, obtained while breathing 6% CO_2 in O_2, the calculated CBF value would be 62.4 ml/100 g/min with 95% confidence limits of $\pm$3.8 ml/100 g/min for an average measurement in several subjects and $\pm$11.5 ml/100 g/min for an individual measurement in one subject.

Relative Changes in CBF and MCA Blood Flow Velocity during Hypercapnia and Hypocapnia in an Oxygen Background

Using as a baseline the measured values of CBF and flow velocity obtained while breathing 100% O_2 at rest, percent changes in both parameters for each subject in the three remaining respiratory conditions are shown in Fig. 5. Percent changes in CBF exceeded corresponding velocity changes for all eight subjects at both of the increased levels of arterial Pco_2. During exposure to hyperventilation hypocapnia, CBF percent decrements were smaller than velocity decrements in seven subjects, while both decrements were nearly equal in one subject. At increased levels of arterial Pco_2, the larger CBF percent increments are consistent with MCA vasodilation in response to hypercapnia (Fig. 5). During exposure to hyperventilation hypocapnia, however, equivalent percent decrements in CBF and velocity would be expected if MCA diameter remained constant, and CBF decrements would be relatively larger in the case of MCA vasoconstriction.

The observation that velocity percent decrements significantly exceeded corresponding CBF decrements during hyperventilation hypocapnia is consistent with earlier associations of cerebral vasodilation with extreme hypocapnic alkalosis (Du Boulay and Symon, 1971; Wollman et al, 1968). In three groups of patients who had undergone carotid angiography under general anesthesia, Du Boulay and Symon (1971) measured the diameters of major cerebral vessels under nearly identical conditions except for the level of controlled ventilation. Reducing arterial Pco_2 from

45 to 29 mm Hg (corresponding to mid-portion of CBF curve in Fig. 2) caused the expected arterial vasoconstriction. However, further arterial Pco_2 reduction to 21 mm Hg was associated with significant MCA vasodilation from 2.83 to 3.21 mm in diameter. This unexpected vasodilation during extreme hypocapnia was later confirmed in baboons under more tightly controlled conditions (Du Boulay and Symon, 1971). Wollman et al. (1968) also studied the CBF effects of extreme respiratory and metabolic alkalosis in anesthetized young men. Intravenous infusion of sodium bicarbonate with arterial Pco_2 controlled at 19 mm Hg significantly increased CBF by 17% from the pre-infusion hypocapnic control level. The mechanism for the paradoxical CBF effects of extreme alkalosis is not known (Heistad and Kontos, 1983; Wollman et al., 1968).

The relationship of MCA diameter to arterial Pco_2 observed by Du Boulay and Symon (1971) can be used to examine the internal consistency of the relative changes in CBF and flow velocity found in the present study. With the aid of a regression equation that describes the stated relationship, MCA diameters of 3.08 mm and 3.29 mm, respectively, are obtained for the arterial Pco_2 levels of 38.5 and 49.9 mm Hg from the present study (Table 1). Over the same range of arterial Pco_2, MCA blood flow velocity increased by an average value of about 63%, while CBF_{15} for the left MCA distribution more than doubled. These relative changes in flow velocity and volume are consistent with an 11% increment in MCA diameter. Starting from a baseline value of 3.08 mm, the calculated MCA diameter at an arterial Pco_2 of 49.9

mm Hg is 3.42 mm, which is similar to the 3.29 mm value obtained from the data of Du Boulay and Symon. During hyperventilation to an arterial Pco_2 of 25.3 mm Hg, the relative decrements in flow velocity and CBF_{15} of about 26% and 16%, respectively, are consistent with MCA vasodilation from a diameter of 3.08 mm to 3.28 mm, which also agrees favorably with the value of 3.21 mm obtained by Du Boulay and Symon at an average arterial Pco_2 of 21.1 mm Hg.

In contrast to the uncertainty regarding the relationship of CBF to arterial Pco_2 during extreme hyperventilation hypocapnia, the CBF response to arterial hypercapnia is well defined (Kety and Schmidt, 1948; Heistad and Kontos, 1983). Using baseline values obtained in the present experiments while breathing 100% O_2 at rest, the relationship of percent change in CBF to percent change in blood flow velocity for increased levels of arterial Pco_2 is defined by a regression line (Fig. 5) with the following equation:

$$\%\Delta CBF = 1.56 \times \%\Delta Velocity$$

This equation, for which SE_{est} is 12.6% and R^2 is 0.92, should be used to estimate relative CBF increments from measured percent changes in MCA blood flow velocity over an arterial Pco_2 range of about 35 to at least 50 mm Hg. The useful range of this relationship should not be extended to more extreme levels of hypocapnia.

The curve shown in Fig. 4 represents CBF and flow velocity data obtained over an arterial Pco_2 range of 25 to 50 mm Hg. Empirically, the 8 points obtained during hyperventilation hypocapnia lie close to the curve, and exclusion of these points has

little effect on the terms of the parabola that describes the remaining 24 points. Therefore, the curve shown is considered to provide a useful analytical description of the CBF to flow velocity relationship over the entire range of arterial Pco_2 that was studied.

Possible Oxygen Effect on CBF_{15}

Our subjects had an average CBF_{15} of 32.1 ml/100 g/min during oxygen breathing at an arterial Pco_2 of 38.5 mm Hg (Table 1). This value is significantly lower than the average CBF_{15} of 47.4 $\pm$ 4.6 ml/100 g/min (mean $\pm$ SD) measured by Obrist (personal communication, 1995) in a group of 42 young men under normoxic conditions at an average arterial Pco_2 of 36.5 mm Hg. Although these comparative values are consistent with hyperoxic cerebral vasoconstriction, such an oxygen effect has not been established in the absence of concurrent changes in arterial Pco_2. Previous measurements of CBF by the Kety-Schmidt N_2O method under normoxic and hyperoxic conditions in the same subjects have shown average decrements ranging from 13-15% at 1.0 ATA (Kety and Schmidt, 1948; Lambertsen et al., 1953) to 25% at 3.5 ATA (Lambertsen et al., 1953), but these changes were associated with varying degrees of spontaneous hypocapnia. When arterial Pco_2 was kept constant at average levels of either 45.0 or 24.4 mm Hg, breathing 80% O_2 at 1.0 atmosphere did not change CBF from normoxic control values (Lambertsen, 1965). Using radioactive microspheres to measure CBF in awake ponies, Busija et al. (1980) also found that normocapnic hyperoxia did not change CBF from normoxic

values.

Even in our subjects, direct measurements of MCA blood flow velocity under both normoxic and hyperoxic conditions do not support an independent CBF reduction by hyperoxia apart from the influence of a concurrent decrease in arterial Pco_2. Average MCA flow velocity during air breathing was 66.5 cm/sec at an average arterial Pco_2 of 42.1 mm Hg (Table 1). During O_2 breathing, arterial Pco_2 decreased to 38.5 mm Hg and MCA flow velocity was significantly reduced by 12.6% to 58.1 cm/sec. The observed velocity decrement can be entirely explained by the concurrent fall in arterial Pco_2 without invoking an independent effect of hyperoxia.

It is possible that at least some of the apparently contradictory data with regard to an O_2 effect on CBF may be explained by the use of different methods to assess cerebral circulatory parameters. The Kety-Schmidt N_2O and ^{133}Xe clearance methods use different diffusible molecules and measure different CBF properties (Young et al., 1995). In addition, the magnitude of a direct oxygen effect on CBF, if present, may vary at different levels of arterial Pco_2 and may be masked at levels where CO_2 effects are dominant. Comparative measurements of CBF_{15} under normoxic and hyperoxic conditions in the same subjects over an appropriate range of arterial Pco_2 are required to resolve these uncertanties.

Applications and Limitations of MCA Blood Flow Velocity as a CBF Index

The data summarized in Fig. 4 indicate that MCA blood flow velocity provides a useful index of CBF over a wide range of arterial Pco_2 in a hyperoxic background.

Transcranial doppler ultrasonography does not require vascular punctures, immobilization of the subject, bulky instrumentation, or administration of radioactive isotopes. Therefore, it can be used under conditions that preclude the use of other methods that measure CBF directly. Furthermore, it is uniquely suitable for measuring rates of cerebral circulatory responses to abruptly imposed physiological or pharmacological stimuli.

With respect to baseline values measured while breathing 100% O_2 at rest, our data are consistent with MCA vasodilation during exposure to both hypercapnia and extreme hyperventilation hypocapnia (Fig. 5). However, it cannot be assumed that the specific relationships of CBF to MCA blood flow velocity shown in Figs. 4 and 5 are fully applicable to other conditions such as hypoxia or exercise, in which changes in MCA diameter might occur. Additional concurrent measurements of CBF and MCA blood flow velocity under such conditions are required to determine the interrelationships of these parameters during exposure to physiological and pharmacological stimuli that differ significantly from those imposed in this study.

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Table 1

CEREBRAL BLOOD FLOW AND FLOW VELOCITY, ARTERIAL OXYGENATION AND ACID-BASE STATE, AND HEMODYNAMIC RESPONSES DURING EXPOSURE TO OXYGEN, CARBON DIOXIDE, AND HYPERVENTILATION

Condition	Arterial Pco_2 (mm Hg)	Arterial pH	Arterial Po_2 (mm Hg)
Air	42.1 ± 2.4	7.402 ± 0.016	95.3 ± 11.3
O_2	38.5 ± 3.5	7.432 ± 0.033	570.8 ± 34.9
O_2/4%CO_2	43.6 ± 2.6	7.390 ± 0.017	570.5 ± 41.0
O_2/6%CO_2	49.9 ± 3.5	7.340 ± 0.016	573.5 ± 42.5
O_2/HV	25.3 ± 3.8	7.584 ± 0.067	585.8 ± 48.8

Condition	TCD-MCA (cm/sec)	CBF_{15}(Global) (ml/100g/min)	F_1(Global) (ml/100g/min)
Air	66.5 ± 7.6	---	---
O_2	58.1 ± 9.9	32.1 ± 5.0	41.7 ± 7.1
O_2/4%CO_2	68.1 ± 11.3	42.3 ± 7.6	59.5 ± 9.9
O_2/6%CO_2	94.2 ± 14.5	65.0 ± 16.1	91.8 ± 19.4
O_2/HV	42.8 ± 5.8	27.2 ± 4.0	35.0 ± 5.7

Condition	Heart Rate (cm/sec)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
Air	60.9 ± 9.0	150.9 ± 8.3	81.6 ± 6.2
O_2	57.3 ± 8.3	144.4 ± 12.0	80.4 ± 5.6
O_2/4%CO_2	61.1 ± 10.5	146.1 ± 11.8	81.1 ± 7.2
O_2/6%CO_2	70.0 ± 11.3	156.4 ± 13.6	84.8 ± 9.8
O_2/HV	65.1 ± 4.6	142.8 ± 17.9	83.6 ± 9.6

Mean Values ± S.D., N = 8, HV = Hyperventilation
TCD = Transcranial Doppler, MCA = Middle Cerebral Artery

{7/95:navy:tcdvscbf:720}

FIGURE LEGENDS

Fig. 1. Experiment protocol for concurrent measurements of CBF and MCA blood flow velocity. Inspired gas mixtures were administered in the order shown. Sampling periods are indicate Background ^{133}Xe counts were monitored for 5 minutes before each period of ^{133}Xe loadin to correct subsequent clearance values for the small amount of ^{133}Xe remaining from the previous CBF determination.

Fig. 2. Average relationships of CBF_{15} index and MCA blood flow velocity to arterial Pco_2 during O_2 breathing at 1.0 ATA. Mean values $\pm$ SD for 8 subjects are shown. Note that units of flow and velocity (on opposite sides of the figure) are identical. Absolute values have not been shifted to make measured average values coincide at any level of arterial Pco_2. Dashed lines on left sides of both curves indicate uncertainty regarding accuracy of interpolated values within hypocapnic range of arterial Pco_2. See text for discussion.

Fig. 3. Individual relationships of CBF_{15} to MCA blood flow velocity in 8 subjects over arterial Pco_2 range of 25 to 50 mm Hg. The individual curves are nearly superimposed for all but one of the 8 subjects. This subject had an average CBF-Pco_2 relationship, but his MCA blood flow velocities were the lowest of all subjects across the entire range of arterial Pco_2. His velocity-Pco_2 relationship was otherwise typical and could be consistent with either an unusually large MCA diameter or an unusually large angle of insonation between transducer probe and MCA axis.

Fig. 4. Parabolic relationship of CBF_{15} to MCA blood flow velocity with 95% confidence limits for average and individual data. Data points are identical to those shown in Fig. 3. Open circles indicate individual values for spontaneous 100% O_2 breathing. See text for equation of the curve.

Fig. 5. Individual relationships of percent change in CBF_{15} to percent change in MCA blood flow velocity. Values obtained while breathing 100% O_2 at rest (open circles in Fig. 4) were used to calculate percent changes in CBF and blood flow velocity (normalized values) for each subject in each of the three remaining conditions. The dashed diagonal represents the line of equal changes for both parameters. The solid line is a regression line through all 16 points obtained at increased levels of arterial Pco_2 with the intercept set at zero. See text for equation of the line. Average percent changes in CBF are significantly larger than corresponding flow velocity changes at both increased levels of arterial Pco_2, and are significantly smaller than percent changes in velocity during exposure to hyperventilation hypocapnia.

Fig. 1

Inspired Gas Condition

1. 100% O_2
2. 4% CO_2 (in O_2)
3. 6% CO_2 (in O_2)
4. 100% O_2 (Hyperventilation)

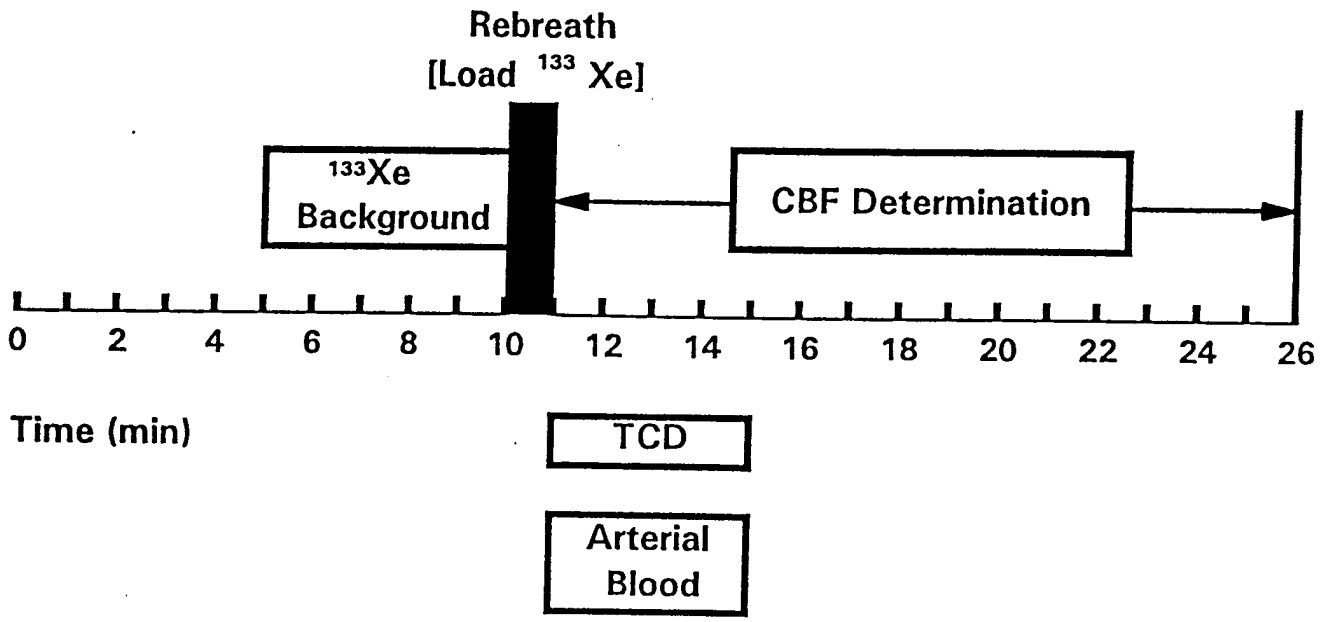
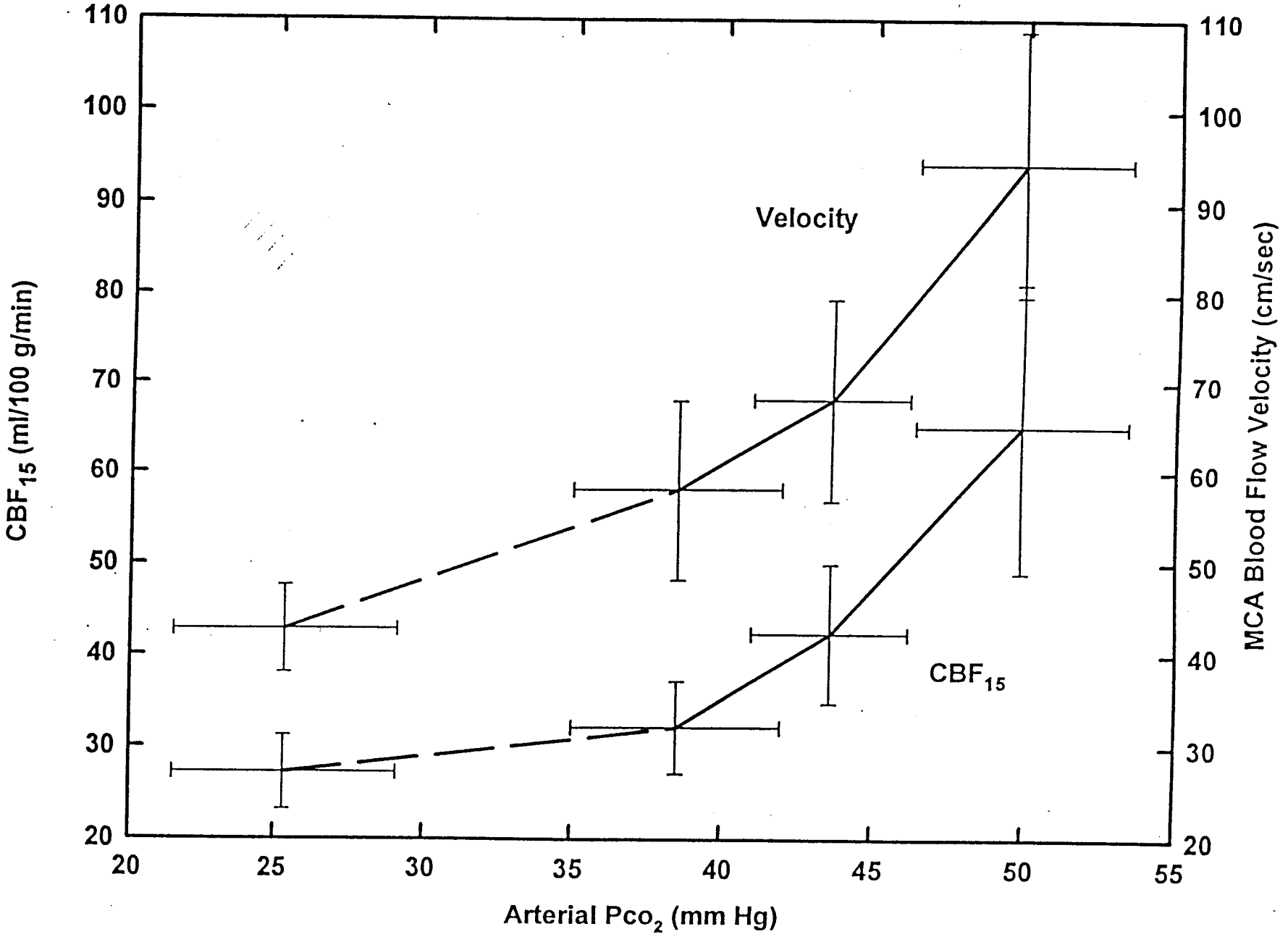


Fig. 2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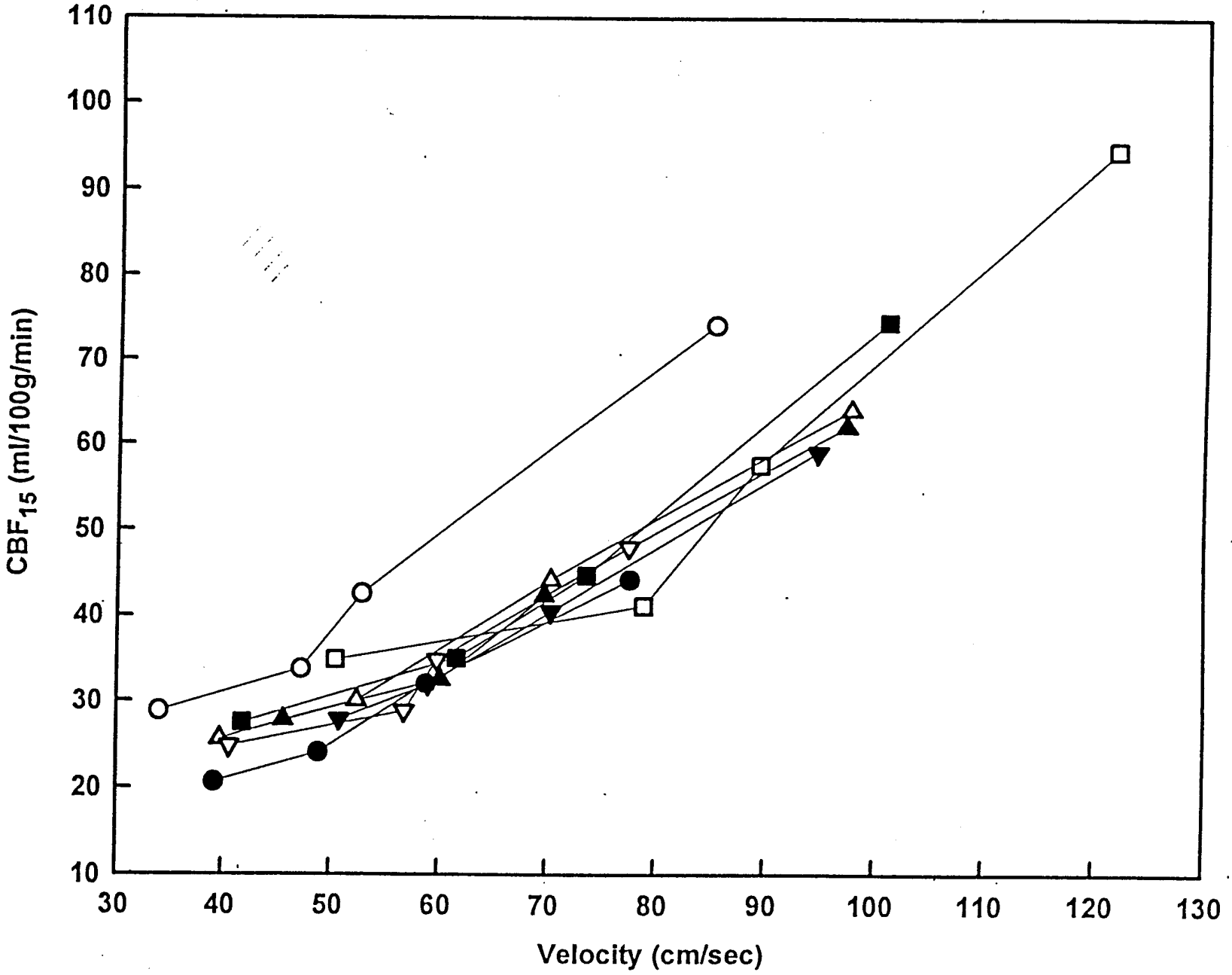
Velocity
CBF15
CBF15 (ml/100 g/min)
MCA Blood Flow Velocity (cm/sec)
Arterial Pco2 (mm Hg)

Fig. 3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CBF15 (ml/100g/min)
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60
70
80
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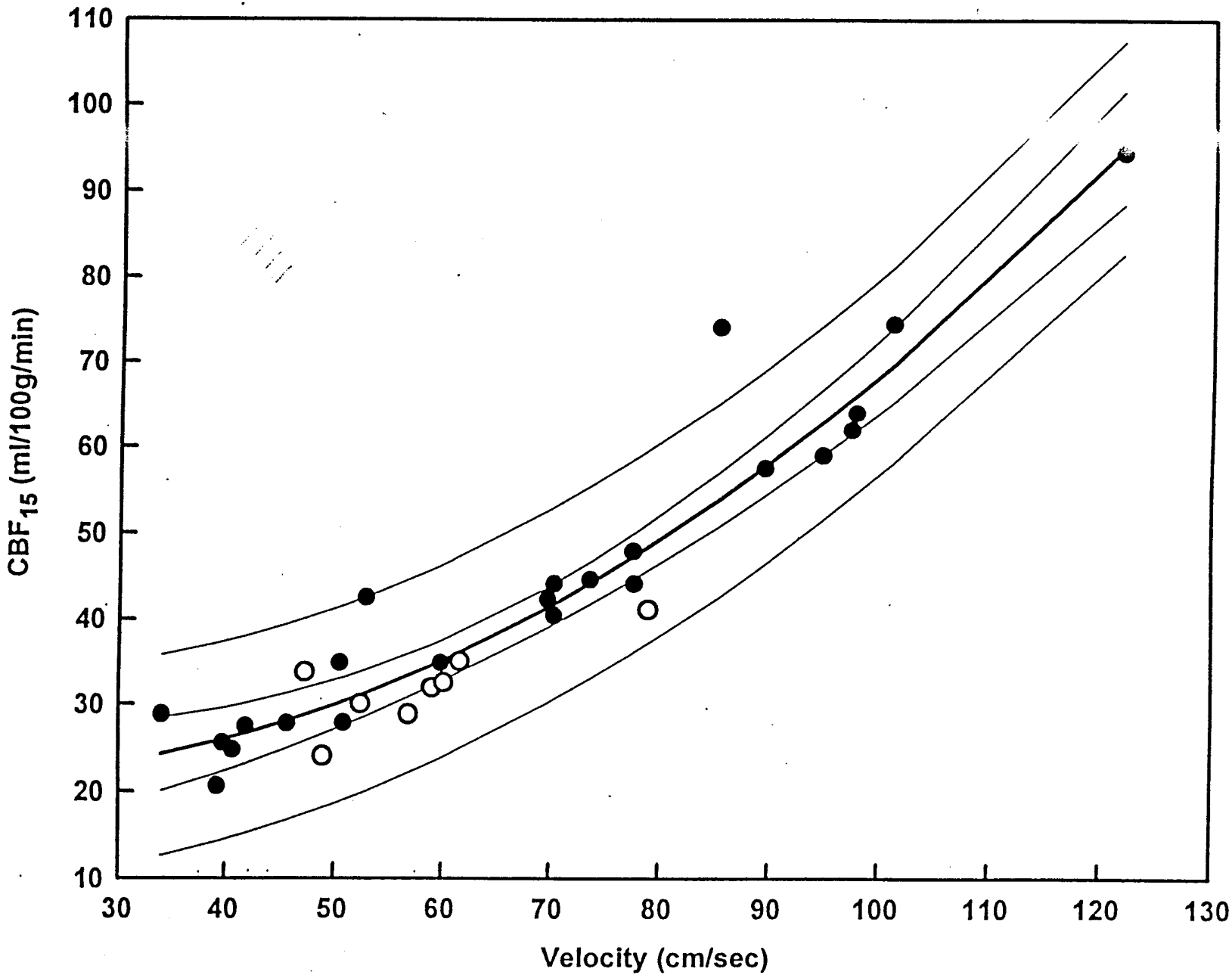
100
110
120
130
Velocity (cm/sec)

Fig. 4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CBF15 (ml/100g/min)
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80
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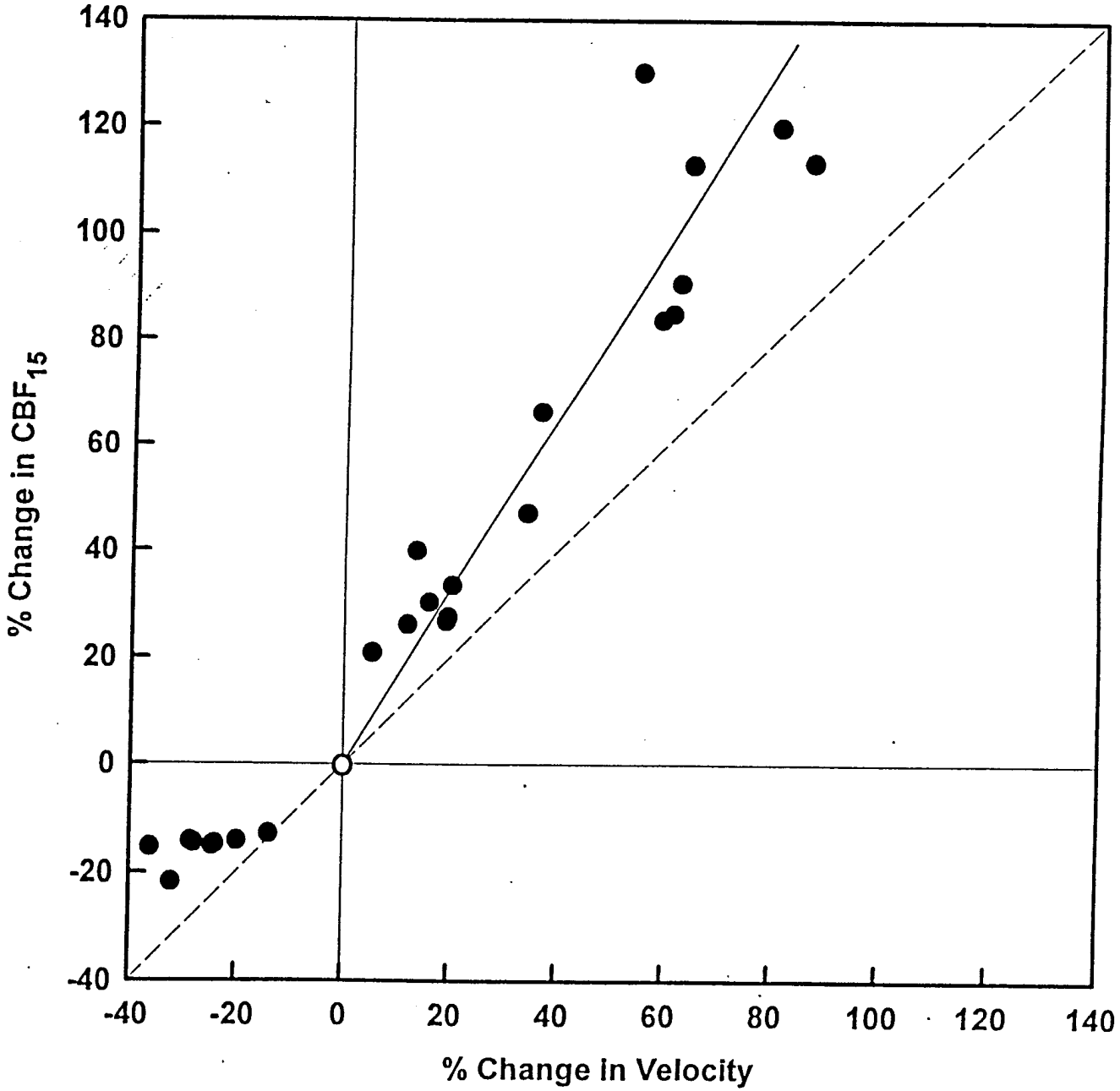
100
110
120
130
Velocity (cm/sec)

Fig. 5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140
% Change in CBF_{15}
% Change in Velocity